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Prevention and Control of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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Prevention and Control of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Summary

This report updates the 2004 recommendations by the Advisory Committee on Immunization Practices (ACIP) regarding the use of influenza vaccine and antiviral agents (CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2004;53[No. RR-6]:1–40). *The 2005 recommendations include new or updated information regarding 1) vaccination of persons with conditions leading to compromise of the respiratory system; 2) vaccination of health-care workers; 3) clarification of the role of live, attenuated influenza vaccine (LAIV) in vaccine shortage situations; 4) the 2005–06 trivalent vaccine virus strains: A/California/7/2004 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Shanghai/361/2002-like antigens (for the A/California/7/2004 [H3N2]-like antigen, manufacturers may use the antigenically equivalent A/New York/55/2004 virus, and for the B/Shanghai/361/2002-like antigen, manufacturers may use the antigenically equivalent B/Jilin/20/2003 virus or B/Jiangsu/10/2003 virus); and 5) the assessment of vaccine supply, timing of influenza vaccination, and prioritization of inactivated vaccine in shortage situations. A link to this report and other information can be accessed at http://www.cdc.gov/flu.*

Introduction

Epidemics of influenza typically occur during the winter months in temperate regions and have been responsible for an average of approximately 36,000 deaths/year in the United States during 1990–1999 (*1*). Influenza viruses also can cause pandemics, during which rates of illness and death from influenza-related complications can increase worldwide. Influenza viruses cause disease among all age groups (*2–4*). Rates of infection are highest among children, but rates of serious illness and death are highest among persons aged ≥65 years, children aged <2 years, and persons of any age who have medical conditions that place them at increased risk for complications from influenza (*2,5–7*).

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Influenza vaccination is the primary method for preventing influenza and its severe complications. In this report from the Advisory Committee on Immunization Practices (ACIP), the primary target groups recommended for annual vaccination are 1) persons at increased risk for influenza-related complications (i.e., those aged ≥65 years, children aged 6–23 months, pregnant women, and persons of any age with certain chronic medical conditions); 2) persons aged 50–64 years because this group has an elevated prevalence of certain chronic medical conditions; and 3) persons who live with or care for persons at high risk (e.g., health-care workers and household contacts who have frequent contact with persons at high risk and who can transmit influenza to those persons at high risk). Vaccination is associated with reductions in influenza-related respiratory illness and physician visits among all age groups, hospitalization and death among persons at high risk, otitis media among children, and work absenteeism among adults (*8–18*). Although influenza vaccination levels increased substantially during the 1990s, further improvements in vaccine coverage levels are needed, chiefly among persons aged <65 years who are at increased risk for influenza-related complications among all racial and ethnic groups, among blacks and Hispanics aged ≥65 years, among children aged 6–23 months,

and among health-care workers. ACIP recommends using strategies to improve vaccination levels, including using reminder/recall systems and standing orders programs (*19–21*). Although influenza vaccination remains the cornerstone for the control and treatment of influenza, information on antiviral medications is also presented because these agents are an adjunct to vaccine.

Primary Changes and Updates in the Recommendations

The 2005 recommendations include five principal changes or updates:

- ACIP recommends that persons with any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration be vaccinated against influenza (see Target Groups for Vaccination).
- ACIP emphasizes that all health-care workers should be vaccinated against influenza annually, and that facilities that employ health-care workers be strongly encouraged to provide vaccine to workers by using approaches that maximize immunization rates.
- Use of both available vaccines (inactivated and LAIV) is encouraged for eligible persons every influenza season, especially persons in recommended target groups. During periods when inactivated vaccine is in short supply, use of LAIV is especially encouraged when feasible for eligible persons (including health-care workers) because use of LAIV by these persons might considerably increase availability of inactivated vaccine for persons in groups at high risk.
- The 2004–05 trivalent vaccine virus strains are A/California/7/2004 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Shanghai/361/2002-like antigens. For the A/California/7/2004 (H3N2)-like antigen, manufacturers may use the antigenically equivalent A/New York/55/2004 virus, and for the B/Shanghai/361/2002-like antigen, manufacturers may use the antigenically equivalent B/Jilin/20/2003 virus or B/Jiangsu/10/2003 virus (see Influenza Vaccine Composition).
- CDC and other agencies will assess the vaccine supply throughout the manufacturing period and will make recommendations preceding the 2005–06 influenza season regarding the need for tiered timing of vaccination of different risk groups. In addition, CDC will publish ACIP recommendations regarding inactivated vaccine subprioritization (tiering) on a later date in *MMWR*.

Influenza and Its Burden

Biology of Influenza

Influenza A and B are the two types of influenza viruses that cause epidemic human disease (*22*). Influenza A viruses are further categorized into subtypes on the basis of two surface antigens: hemagglutinin and neuraminidase. Influenza B viruses are not categorized into subtypes. Since 1977, influenza A (H1N1) viruses, influenza A (H3N2) viruses, and influenza B viruses have been in global circulation. In 2001, influenza A (H1N2) viruses that probably emerged after genetic reassortment between human A (H3N2) and A (H1N1) viruses began circulating widely. Both influenza A and B viruses are further separated into groups on the basis of antigenic characteristics. New influenza virus variants result from frequent antigenic change (i.e., antigenic drift) resulting from point mutations that occur during viral replication. Influenza B viruses undergo antigenic drift less rapidly than influenza A viruses.

Immunity to the surface antigens, particularly the hemagglutinin, reduces the likelihood of infection and severity of disease if infection occurs (*23*). Antibody against one influenza virus type or subtype confers limited or no protection against another type or subtype of influenza. Furthermore, antibody to one antigenic variant of influenza virus might not completely protect against a new antigenic variant of the same type or subtype (*24*). Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual incorporation of one or more new strains in each year's influenza vaccine.

Clinical Signs and Symptoms of Influenza

Influenza viruses are spread from person to person primarily through the coughing and sneezing of infected persons (*22*). The typical incubation period for influenza is 1–4 days, with an average of 2 days (*25*). Adults can be infectious from the day before symptoms begin through approximately 5 days after illness onset. Children can be infectious for ≥10 days, and young children can shed virus for several days before their illness onset. Severely immunocompromised persons can shed virus for weeks or months (*26–29*).

Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis) (*30*). Among children, otitis media, nausea, and vomiting are also commonly reported with influenza illness (*31–33*). Respiratory illness caused by influenza is difficult to distinguish from illness caused by other respiratory pathogens on the basis of symptoms alone (see Role of Laboratory Diagnosis). Reported sensitivities and speci-

ficities of clinical definitions for influenza-like illness (ILI) in studies primarily among adults that include fever and cough have ranged from 63% to 78% and 55% to 71%, respectively, compared with viral culture (*34,35*). Sensitivity and predictive value of clinical definitions can vary, depending on the degree of co-circulation of other respiratory pathogens and the level of influenza activity (*36*). A study among older nonhospitalized patients determined that symptoms of fever, cough, and acute onset had a positive predictive value of 30% for influenza (*37*), whereas a study of hospitalized older patients with chronic cardiopulmonary disease determined that a combination of fever, cough, and illness of <7 days was 78% sensitive and 73% specific for influenza (*38*). However, a study among vaccinated older persons with chronic lung disease reported that cough was not predictive of influenza infection, although having a fever or feverishness was 68% sensitive and 54% specific for influenza infection (*39*).

Influenza illness typically resolves after 3–7 days for the majority of persons, although cough and malaise can persist for >2 weeks. Among certain persons, influenza can exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease), lead to secondary bacterial pneumonia or primary influenza viral pneumonia, or occur as part of a coinfection with other viral or bacterial pathogens (*40*). Young children with influenza infection can have initial symptoms mimicking bacterial sepsis with high fevers (*41,42*), and ≤20% of children hospitalized with influenza can have febrile seizures (*32,43*). Influenza infection has also been associated with encephalopathy, transverse myelitis, Reye syndrome, myositis, myocarditis, and pericarditis (*32,40,44,45*).

Hospitalizations and Deaths from Influenza

The risks for complications, hospitalizations, and deaths from influenza are higher among persons aged ≥65 years, young children, and persons of any age with certain underlying health conditions (see Persons at Increased Risk for Complications) than among healthy older children and younger adults (*1,6,8,46–52*). Estimated rates of influenza-associated hospitalizations have varied substantially by age group in studies conducted during different influenza epidemics (Table 1).

Among children aged 0–4 years, hospitalization rates have ranged from approximately 500/100,000 children for those with high-risk medical conditions to 100/100,000 children for those without high-risk medical conditions (*53–56*). Within the 0–4 year age group, hospitalization rates are highest among children aged 0–1 years and are comparable to rates reported among persons aged ≥65 years (*55,56*) (Table 1).

During influenza epidemics from 1979–80 through 2000–01, the estimated overall number of influenza-associated hospitalizations in the United States ranged from approximately 54,000 to 430,000/epidemic. An average of approximately 226,000 influenza-related excess hospitalizations occurred per year, with 63% of all hospitalizations occurring among persons aged ≥65 years (*57*). Since the 1968 influenza A (H3N2) virus pandemic, the greatest numbers of influenza-associated hospitalizations have occurred during epidemics caused by type A (H3N2) viruses (*58*).

Influenza-related deaths can result from pneumonia and from exacerbations of cardiopulmonary conditions and other chronic diseases. Deaths of older adults account for ≥90% of deaths attributed to pneumonia and influenza (*1,52*). In one study of influenza epidemics, approximately 19,000 influenza-associated pulmonary and circulatory deaths per influenza season occurred during 1976–1990, compared with approximately 36,000 deaths during 1990–1999 (*1*). Estimated rates of influenza-associated pulmonary and circulatory deaths/100,000 persons were 0.4–0.6 among persons aged 0–49 years, 7.5 among persons aged 50–64 years, and 98.3 among persons aged ≥65 years. In the United States, the number of influenza-associated deaths might be increasing in part because the number of older persons is increasing (*59*). In addition, influenza seasons in which influenza A (H3N2) viruses predominate are associated with higher mortality (*60*); influenza A (H3N2) viruses predominated in 90% of influenza seasons during 1990–1999, compared with 57% of seasons during 1976–1990 (*1*).

Deaths from influenza are uncommon among both children with and without high-risk conditions, but do occur (*61,62*). A study that modeled influenza-related deaths estimated that an average of 92 deaths (0.4 deaths per 100,000) occurred among children aged <5 years annually during the 1990's, compared with 32,651 deaths (98.3 per 100,000) among adults aged ≥65 years (*1*). Reports of 153 laboratory-confirmed influenza-related pediatric deaths from 40 states during the 2003–04 influenza season indicated that 61 (40%) were aged <2 years and, of 92 children aged 2–17 years, 64 (70%) did not have an underlying medical condition traditionally considered to place a person at risk for influenza-related complications (CDC, National Center for Infectious Diseases, unpublished data, 2005). Further information is needed regarding the risk for severe influenza-complications and optimal strategies for minimizing severe disease and death among children.

Options for Controlling Influenza

In the United States, the primary option for reducing the effect of influenza is immunoprophylaxis with vaccine. Inactivated (i.e., killed virus) influenza vaccine and live, attenuated influenza vaccine are available for use in the United States (see Recommendations for Using Inactivated and Live, At-

TABLE 1. Estimated rates of influenza-associated hospitalization, by age group and risk group for selected studies* — United States

Study years	Population	Age group	Hospitalizations/ 100,000 persons with high-risk conditions	Hospitalizations/ 100,000 persons without high-risk conditions
1973–1993† § ¶	Tennessee Medicaid	0–11 mos	1,900	496–1,038**
		1–2 yrs	800	186
		3–4 yrs	320	86
		5–14 yrs	92	41
1992–1997†† §§	Two health maintenance organizations	0–23 mos		144–187
		2–4 yrs		0–25
		5–17 yrs		8–12
1968–1969, 1970–1971, 1972–1973¶¶ ***	Health maintenance organization	15–44 yrs	56–110	23–25
		45–64 yrs	392–635	13–23
		≥65 yrs	399–518	—
1969–1995*** †††	National Hospital Discharge Data	<65 yrs	—	20–42§§§ ¶¶¶
1969–1995*** †††		≥65 yrs	—	125–228¶¶¶
1979–2001**** ††††	National Hospital Discharge Data	All ages	—	88.4§§§§

* Rates were estimated in years and populations with low vaccination rates. Hospitalization rates can be expected to decrease as vaccination rates increase. Vaccination can be expected to reduce influenza-related hospitalizations by 30%–70% among older persons and likely by even higher percentages among younger age groups when vaccine and circulating influenza virus strains are antigenically similar.

† **Source:** Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Griffin MR. Effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med 2000;342:225–31.

§ Outcomes were for acute cardiac or pulmonary conditions.

¶ **Source:** Neuzil KM, Wright PF, Mitchel EF, Griffin MR. Burden of influenza illness in children with asthma and other chronic medical conditions. J Pediatr 2000;137:856–64.

** The low estimate is for infants aged 6–11 months, and the high estimate is for infants aged 0–5 months.

†† **Source:** Izurieta HA, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med 2000;342:232–9.

§§ Outcomes were for acute pulmonary conditions. Influenza-attributable hospitalization rates for children at high risk were not included in this study.

¶¶ **Source:** Barker WH, Mullooly JP. Impact of epidemic type A influenza in a defined adult population. Am J Epidemiol 1980;112:798–811.

*** Outcomes were limited to hospitalizations in which either pneumonia or influenza was listed as the first condition on discharge records (Simonsen) or included anywhere in the list of discharge diagnoses (Barker).

††† **Source:** Simonsen L, Fukuda K, Schonberger LB, Cox NJ. Impact of influenza epidemics on hospitalizations. J Infect Dis 2000;181:831–7.

§§§ Persons at high risk and not at high risk for influenza-related complications are combined.

¶¶¶ The low estimate is the average during influenza A (H1N1) or influenza B-predominate seasons, and the high estimate is the average during influenza A (H3N2)-predominate seasons.

****Outcomes were for rate of primary respiratory and circulatory hospitalizations.

†††† **Source:** Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA 2004;292:1333–40.

§§§§ Rate for all ages of persons, both with and without high-risk conditions.

tenuated Influenza Vaccine). Vaccinating persons at high risk for complications and their contacts each year before seasonal increases in influenza virus circulation is the most effective means of reducing the effect of influenza. Vaccination coverage can be increased by administering vaccine to persons during hospitalizations or routine health-care visits before the influenza season, making special visits to physicians' offices or clinics unnecessary. When vaccine and epidemic strains are well-matched, achieving increased vaccination rates among persons living in closed settings (e.g., nursing homes and other chronic-care facilities) and among staff can reduce the risk for outbreaks by inducing herd immunity (*13*). Vaccination of health-care workers and other persons in close contact with persons at increased risk for severe influenza illness can also reduce transmission of influenza and subsequent influenza-related complications. Antiviral drugs used for chemoprophylaxis or treatment of influenza are a key adjunct to vaccine (see Recommendations for Using Antiviral Agents for Influenza). However, antiviral medications are not a substitute for vaccination.

Influenza Vaccine Composition

Both the inactivated and live, attenuated vaccines prepared for the 2005–06 season will include A/California/7/2004 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Shanghai/361/2002-like antigens. For the A/California/7/2004 (H3N2)-like antigen, manufacturers may use the antigenically equivalent A/New York/55/2004 (H3N2) virus, and

for the B/Shanghai/361/2002-like antigen, manufacturers may use the antigenically equivalent B/Jilin/20/2003 virus or B/Jiangsu/10/2003 virus. These viruses will be used because of their growth properties and because they are representative of influenza viruses likely to circulate in the United States during the 2005–06 influenza season. Because circulating influenza A (H1N2) viruses are a reassortant of influenza A (H1N1) and (H3N2) viruses, antibody directed against influenza A (H1N1) and influenza (H3N2) vaccine strains provides protection against circulating influenza A (H1N2) viruses. Influenza viruses for both the inactivated and live attenuated influenza vaccines are initially grown in embryonated hens eggs. Thus, both vaccines might contain limited amounts of residual egg protein.

For the inactivated vaccine, the vaccine viruses are made noninfectious (i.e., inactivated or killed) (*63*). Subvirion and purified surface antigen preparations of the inactivated vaccine are available. Manufacturing processes differ by manufacturer. Manufacturers might use different compounds to inactivate influenza viruses and add antibiotics to prevent bacterial contamination. Package inserts should be consulted for additional information.

Thimerosal

Thimerosal, a mercury-containing compound, has been used as a preservative in vaccines (*64*) since the 1930s and is used in multi-dose vials of inactivated influenza vaccine to reduce the likelihood of bacterial contamination. Although no scientific evidence indicates that thimerosal in vaccines leads to serious adverse events in vaccine recipients, in 1999, the U.S. Public Health Service and other organizations recommended that efforts be made to eliminate or reduce the thimerosal content in vaccines to decrease total mercury exposure, chiefly among infants (*64–66*). Since mid-2001, vaccines routinely recommended for infants in the United States have been manufactured either without or with only trace amounts of thimerosal to provide a substantial reduction in the total mercury exposure from vaccines for children (*67*). Vaccines containing trace amounts of thimerosal have <1 mcg mercury/dose.

Influenza Vaccines and Thimerosal. LAIV does not contain thimerosal. Thimerosal preservative-containing inactivated influenza vaccines, distributed in multi-dose containers in the United States, contain 25 mcg of mercury/0.5-mL dose (*64,65*). Inactivated influenza virus vaccines distributed in the United States will also be available in 2005 in a *thimerosal-free* formulation in both 0.25 mL and 0.5-mL single-dose syringes and a preservative-free formulation (which contains trace amounts of thimerosal) in 0.25-mL–dose syringes.

Influenza vaccine is part of the routine childhood immunization schedule. Sanofi Pasteur, Inc. (formerly Aventis Pasteur, Inc.) produces FluZone®, which is an inactivated influenza vaccine approved by the Food and Drug Administration (FDA) for persons aged ≥6 months. FluZone that is available in multi-dose vials contains thimerosal as a preservative. Thimerosal-free FluZone packaged as 0.25-mL unit dose syringes is available for use among persons aged 6–35 months. Thimerosal-free FluZone packaged as 0.5 mL unit dose syringes is available for use among persons aged ≥3 years. Fluvirin®, produced by Chiron, is an inactivated influenza vaccine available in a preservative-free formulation, is packaged as 0.5-mL single-dose syringes, and is licensed for use in persons aged ≥4 years. The preservative-free Fluvirin vaccine contains trace amounts of thimerosal. The total amount of inactivated influenza vaccine available without thimerosal as a preservative will be increased as manufacturing capabilities are expanded.

The risks for severe illness from influenza infection are elevated among both young children and pregnant women, and both groups benefit from vaccination by preventing illness and death from influenza. In contrast, no scientifically conclusive evidence exists of harm from exposure to thimerosal preservative-containing vaccine, whereas evidence is accumulating of lack of any harm resulting from exposure to such vaccines (*64,68*). Therefore, the benefits of influenza vaccination outweigh the theoretical risk, if any, for thimerosal exposure through vaccination. Nonetheless, certain persons remain concerned regarding exposure to thimerosal. The U.S. vaccine supply for infants and pregnant women is in a period of transition during which the availability of thimerosal-reduced or thimerosal-free vaccine intended for these groups is being expanded by manufacturers as a feasible means of reducing an infant's total exposure to mercury because other environmental sources of exposure are more difficult or impossible to eliminate. Reductions in thimerosal in other vaccines have been achieved already and have resulted in substantially lowered cumulative exposure to thimerosal from vaccination among infants and children. For all of these reasons, persons recommended to receive inactivated influenza vaccine may receive either vaccine preparation, depending on availability.

Efficacy and Effectiveness of Inactivated Influenza Vaccine

The effectiveness of inactivated influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation. The majority of vaccinated children and young adults develop high postvaccination hemagglutination inhibition antibody titers (*69–71*). These antibody titers are protective against illness caused by

strains that are antigenically similar to those strains of the same type or subtype included in the vaccine (*70–73*).

Adults Aged <65 Years. When the vaccine and circulating viruses are antigenically similar, influenza vaccine prevents influenza illness among approximately 70%–90% of healthy adults aged <65 years (*9,12,74,75*). Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health-care resources, including use of antibiotics, when the vaccine and circulating viruses are well-matched (*9–12,75,76*). In a case-control study of adults aged 50–64 years with laboratory-confirmed influenza during the 2003–04 season when the vaccine and circulating viruses were not well matched, vaccine effectiveness was estimated to be 52% among healthy persons and 38% among those with one or more high-risk conditions (*77*).

Children. Children aged 6 months can develop protective levels of anti-influenza antibody against specific influenza virus strains after influenza vaccination (*69,70,78–81*), although the antibody response among children at high risk for influenza-related complications might be lower than among healthy children (*82,83*). In a randomized study among children aged 1–15 years, inactivated influenza vaccine was 77%–91% effective against influenza respiratory illness and was 44%–49%, 74%–76%, and 70%–81% effective against influenza seroconversion among children aged 1–5, 6–10, and 11–15 years, respectively (*71*). One study (*84*) reported a vaccine efficacy of 56% against influenza illness among healthy children aged 3–9 years, and another study (*85*) determined vaccine efficacy of 22%–54% and 60%–78% among children with asthma aged 2–6 years and 7–14 years, respectively. A 2-year randomized study of children aged 6–24 months determined that ≥89% of children seroconverted to all three vaccine strains during both years (*86*). During year 1, among 411 children, vaccine efficacy was 66% (95% confidence interval [CI] = 34%–82%) against culture-confirmed influenza (attack rates: 5.5% and 15.9% among vaccine and placebo groups, respectively). During year 2, among 375 children, vaccine efficacy was –7% (95% CI = –247%–67%; attack rates: 3.6% and 3.3% among vaccine and placebo groups, respectively; the second year exhibited lower attack rates overall and was considered a mild season). However, no overall reduction in otitis media was reported. Other studies report that trivalent inactivated influenza vaccine decreases the incidence of influenza-associated otitis media among young children by approximately 30% (*16,17*). A retrospective study among approximately 5,000 children aged 6–23 months conducted during a year with a suboptimal vaccine match indicated vaccine effectiveness of 49% against medically attended, clinically diagnosed pneumonia or influenza (*International Classification of Diseases, Ninth Revision* [ICD-9] codes 480–487) among children who had received 2 doses of influenza vaccine. No effectiveness was demonstrated among children who had received only 1 dose of influenza vaccine, illustrating the importance of administering 2 doses of vaccine to previously unvaccinated children aged <9 years (*87*).

Adults Aged ≥65 Years. Older persons and persons with certain chronic diseases might develop lower postvaccination antibody titers than healthy young adults and thus can remain susceptible to influenza infection and influenza-related upper respiratory tract illness (*88–90*). A randomized trial among noninstitutionalized persons aged ≥60 years reported a vaccine efficacy of 58% against influenza respiratory illness, but indicated that efficacy might be lower among those aged ≥70 years (*91*). The vaccine can also be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death among adults aged ≥65 years with and without high-risk medical conditions (e.g., heart disease and diabetes) (*13–15,18,92*). Among elderly persons not living in nursing homes or similar chronic-care facilities, influenza vaccine is 30%–70% effective in preventing hospitalization for pneumonia and influenza (*15,93*). Among older persons who do reside in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications, and deaths. Among this population, the vaccine can be 50%–60% effective in preventing influenza-related hospitalization or pneumonia and 80% effective in preventing influenza-related death, although the effectiveness in preventing influenza illness often ranges from 30% to 40% (*94–96*).

Efficacy and Effectiveness of LAIV

Healthy Children. A randomized, double-blind, placebo-controlled trial among 1,602 healthy children initially aged 15–71 months assessed the efficacy of trivalent LAIV against culture-confirmed influenza during two seasons (*97,98*). This trial included subsets of 238 healthy children (163 vaccinees and 75 placebo recipients) aged 60–71 months who received 2 doses and 74 children (54 vaccinees and 20 placebo recipients) aged 60–71 months who received a single dose during season one, and a subset of 544 children (375 vaccinees and 169 placebo recipients) aged 60–84 months during season two. Children who continued in the study remained in the same study group. In season one, when vaccine and circulating virus strains were well-matched, efficacy was 93% for all participants, regardless of age, among persons receiving 2 doses of LAIV. Efficacy was 87% in the 60–71-month subset for those who received 2 doses, and was 91% in the subset for those who received 1 or 2 doses. In season two, when the A (H3N2) component was not well-matched between vaccine and circulating virus strains, efficacy was 86% overall and 87% among those aged 60–84 months. The vaccine was 92% effi-

cacious in preventing culture-confirmed influenza during the two-season study. Other results included a 27% reduction in febrile otitis media and a 28% reduction in otitis media with concomitant antibiotic use. Receipt of LAIV also resulted in a 30% lower incidence of febrile otitis media and 21% fewer febrile illnesses. Another study assessing LAIV effectiveness in children aged 18 months–18 years indicated effectiveness against medically attended acute respiratory illness (MAARI) of 18%. However, applying a validation sample of surveillance cultures with MAARI demonstrated efficacy of 92% against influenza A (H1N1) and 66% against an influenza B drift variant (*99*).

Healthy Adults. A randomized, double-blind, placebo-controlled trial among 4,561 healthy working adults aged 18–64 years assessed multiple endpoints, including reductions in illness, absenteeism, health-care visits, and medication use during peak and total influenza outbreak periods (*100*). The study was conducted during the 1997–98 influenza season, when the vaccine and circulating A (H3N2) strains were not well-matched. The study did not include testing of viruses by a laboratory. During peak outbreak periods, no difference was identified between LAIV and placebo recipients experiencing any febrile episodes. However, vaccination was associated with reductions in severe febrile illnesses of 19% and febrile upper respiratory tract illnesses of 24%. Vaccination also was associated with fewer days of illness, fewer days of work lost, fewer days with health-care–provider visits, and reduced use of prescription antibiotics and over-the-counter medications.

Among the subset of 3,637 healthy adults aged 18–49 years, LAIV recipients (n = 2,411) had 26% fewer febrile upper-respiratory illness episodes; 27% fewer lost work days as a result of febrile upper respiratory illness; and 18%–37% fewer days of health-care provider visits caused by febrile illness, compared with placebo recipients (n = 1,226). Days of antibiotic use were reduced by 41%–45% in this age subset.

Another randomized, double-blind, placebo-controlled challenge study among 92 healthy adults (LAIV, n = 29; placebo, n = 31; inactivated influenza vaccine, n = 32) aged 18–41 years assessed the efficacy of both LAIV and inactivated vaccine (*101*). The overall efficacy of LAIV and inactivated influenza vaccine in preventing laboratory-documented influenza from all three influenza strains combined was 85% and 71%, respectively, on the basis of experimental challenge by viruses to which study participants were susceptible before vaccination. The difference in efficacy between the two vaccines was not statistically significant.

Cost-Effectiveness of Influenza Vaccine

Influenza vaccination can reduce both health-care costs and productivity losses associated with influenza illness. Economic studies of influenza vaccination of persons aged ≥65 years conducted in the United States have reported overall societal cost savings and substantial reductions in hospitalization and death (*15,93,102*). Studies of adults aged <65 years have reported that vaccination can reduce both direct medical costs and indirect costs from work absenteeism (*8,10–12,75,103*). Reductions of 13%–44% in health-care–provider visits, 18%–45% in lost workdays, 18%–28% in days working with reduced effectiveness, and 25% in antibiotic use for influenza-associated illnesses have been reported (*10,12,104,105*). One cost-effectiveness analysis estimated a cost of approximately $60–$4,000/illness averted among healthy persons aged 18–64 years, depending on the cost of vaccination, the influenza attack rate, and vaccine effectiveness against ILI (*75*). Another cost-benefit economic study estimated an average annual savings of $13.66/person vaccinated (*106*). In the second study, 78% of all costs prevented were costs from lost work productivity, whereas the first study did not include productivity losses from influenza illness. Economic studies specifically evaluating the cost-effectiveness of vaccinating persons aged 50–64 years are not available, and the number of studies that examine the economics of routinely vaccinating children with inactivated or live, attenuated vaccine are limited (*8,107–110*). However, in a study of inactivated vaccine that included all age groups, cost utility (i.e., cost per year of healthy life gained) improved with increasing age and among those with chronic medical conditions (*8*). Among persons aged ≥65 years, vaccination resulted in a net savings per quality-adjusted life year (QALY) gained and resulted in costs of $23–$256/QALY among younger age groups. Additional studies of the relative cost-effectiveness and cost utility of influenza vaccination among children and among adults aged <65 years are needed and should be designed to account for year-to-year variations in influenza attack rates, illness severity, and vaccine efficacy when evaluating the long-term costs and benefits of annual vaccination.

Vaccination Coverage Levels

One of the national health objectives for 2010 is to achieve vaccination coverage for 90% of persons aged ≥65 years (objective no. 14-29a) (*111*). Among persons aged ≥65 years, influenza vaccination levels increased from 33% in 1989 (*112*) to 66% in 1999 (*113*), surpassing the *Healthy People 2000* objective of 60% (*114*). Vaccine coverage in this group reached the highest levels recorded (68%) during the 1999–00 influenza season, using the percentage of adults reporting influenza vaccination during the previous 12 months who participated in the National Health Interview Survey (NHIS) during the first and second quarters of each calendar year as a proxy measure of influenza vaccine coverage for the previous

influenza season (*113*). Possible reasons for the increase in influenza vaccination levels among persons aged ≥65 years through the 1999–00 influenza season include 1) greater acceptance of preventive medical services by practitioners; 2) increased delivery and administration of vaccine by health-care providers and sources other than physicians; 3) new information regarding influenza vaccine effectiveness, cost-effectiveness, and safety; and 4) initiation of Medicare reimbursement for influenza vaccination in 1993 (*8,14,15,94,95,115,116*). Vaccine coverage increased more rapidly through the mid-1990s than during subsequent seasons (average annual percentage increase of 4% from 1988–89 to 1996–97 versus 1% from 1996–97 to 1999–00) and has remained relatively stable since 2000.

Estimated national influenza vaccine coverage in 2003 among persons aged ≥65 years and 50–64 years was 66% and 37%, respectively, based on 2003 NHIS data (Table 2). The estimated vaccination coverage among adults with high-risk conditions aged 18–49 years and 50–64 years was 24% and 46%, respectively, substantially lower than the *Healthy People 2000* and *2010* objective of 60% (*111,114*). Continued annual monitoring is needed to determine the effects of vaccine supply delays and shortages, changes in influenza vaccination recommendations and target groups for vaccination, reimbursement rates for vaccine and vaccine administration, and other factors related to vaccination coverage among adults and children. New strategies to improve coverage will be needed to achieve the *Healthy People 2010* objective (*21*).

Reducing racial and ethnic health disparities, including disparities in vaccination coverage, is an overarching national goal (*111*). Although estimated influenza vaccination coverage for the 1999–00 season reached the highest levels recorded among older black, Hispanic, and white populations, vaccination levels among blacks and Hispanics continue to lag behind those among whites (*113,117*). Estimated vaccination coverage levels based on 2003 NHIS data among persons aged ≥65 years were 69% among non-Hispanic whites, 48% among non-Hispanic blacks, and 45% among Hispanics (CDC, National Immunization Program, unpublished data, 2005). Additional strate-

TABLE 2. Influenza vaccination coverage rates among adult target* population groups — National Health Interview Survey (NHIS), United States, 2003

Population group	Crude sample size	Weighted sample size	Influenza vaccination rate %	(95% CI†)
All aged 50–64 yrs	6,666	46,000,500	36.8	(35.4–38.2)
All aged ≥65 yrs	5,662	33,677,900	65.5	(64.1–66.9)
Persons with high-risk conditions§				
Aged 18–64 yrs	4,347	29,746,400	34.2	(32.5–35.9)
Aged 18–49 yrs	2,341	16,324,700	24.2	(22.1–26.4)
Aged 50–64 yrs	2,006	13,421,800	46.3	(43.7–49.0)
Persons without high-risk conditions§				
Aged 18–49 yrs	15,654	113,504,600	15.8	(15.1–16.5)
Aged 50–64 yrs	4,637	32,425,100	32.7	(31.2–34.3)
Pregnant women¶	315	2,339,600	12.8	(9.0–17.9)
Health-care workers**	2,146	14,604,000	40.1	(37.5–42.7)
Household contacts of persons at high risk, including children aged <2 yrs††				
Aged 18–49 yrs	2,501	20,404,000	14.9	(13.4–16.6)
Aged 50–64 yrs	489	4,113,400	38.4	(33.6–43.5)

* As recommended by the Advisory Committee on Immunization Practices.

† Confidence interval.

§ Persons categorized as being at high risk for influenza-related complications self-reported one or more of the following: 1) ever being told by a physician they had diabetes, emphysema, coronary heart disease, angina, heart attack, or other heart condition; 2) having a diagnosis of cancer during the previous 12 months (excluding nonmelanoma skin cancer) or ever being told by a physician they have lymphoma, leukemia, or blood cancer during the previous 12 months; 3) being told by a physician they have chronic bronchitis or weak or failing kidneys; or 4) reporting an asthma episode or attack during the preceding 12 months.

¶ Aged 18–44 years, pregnant at the time of the survey and without high-risk conditions.

** Adults were classified as health-care workers if they were currently employed in a health-care occupation or in a health-care–industry setting, on the basis of standard occupation and industry categories recoded in groups by CDC's National Center for Health Statistics.

†† Interviewed adult in each household containing at least one of the following: a child aged <2 years, an adult aged ≥65 years, or any person aged 2–17 years at high risk (see previous footnote §). To obtain information on household composition and high-risk status of household members, the sampled adult, child, and person files from NHIS were merged. Interviewed adults who were health-care workers or who had high-risk conditions were excluded. Information could not be assessed regarding high-risk status of other adults aged 18–64 years in the household, thus, certain adults 18–64 years who live with an adult aged 18–64 years at high risk were not included in the analysis.

gies are needed to achieve the *Healthy People 2010* objectives among all racial and ethnic groups.

In 1997 and 1998, vaccination coverage estimates among nursing home residents were 64%–82% and 83%, respectively (*118,119*). The *Healthy People 2010* goal is to achieve influenza vaccination of 90% among nursing home residents, an increase from the *Healthy People 2000* goal of 80% (*111,114*).

Reported vaccination levels are low among children at increased risk for influenza complications. One study conducted among patients in health maintenance organizations reported influenza vaccination percentages ranging from 9% to 10% among children with asthma (*120*). A 25% vaccination level was reported among children with severe to moderate asthma who attended an allergy and immunology clinic (*121*). However, a study conducted in a pediatric clinic demonstrated an increase in the vaccination percentage of children with asthma or reactive airways disease from 5% to 32% after implementing a reminder/recall system (*122*). One study reported 79% vaccination coverage among children attending a cystic fibrosis treatment center (*123*). Data from BRFSS collected in February 2005 indicated 48% vaccination coverage for 1 or more doses among children aged 6–23 months and 35% coverage among children aged 2–17 years who had one or more high-risk medical conditions during the 2004–05 season (*124*). Increasing vaccination coverage among persons who have high-risk conditions and are aged <65 years, including children at high risk, is the highest priority for expanding influenza vaccine use.

Annual vaccination is recommended for health-care workers. Nonetheless, NHIS reported vaccination coverage of only 40% among health-care workers in the 2003 survey (CDC, National Immunization Program, unpublished data, 2005). Vaccination of health-care workers has been associated with reduced work absenteeism (*9*) and fewer deaths among nursing home patients (*125,126*) and is a high priority for reducing the impact of influenza in health-care settings and for expanding influenza vaccine use (*127,128*).

Limited information is available regarding use of influenza vaccine among pregnant women. Among women aged 18–44 years without diabetes responding to the 2001 BRFSS, those who were pregnant were less likely to report influenza vaccination during the previous 12 months (13.7%) than those not pregnant (16.8%) (*122,129*). Only 13% of pregnant women reported vaccination according to 2003 NHIS data, excluding pregnant women who reported diabetes, heart disease, lung disease, and other selected high-risk conditions (CDC, National Immunization Program, unpublished data, 2004) (Table 2). These data indicate low compliance with the ACIP recommendations for pregnant women. In a study of influenza vaccine acceptance by pregnant women, 71% who were offered the vaccine chose to be vaccinated (*130*). However, a 1999 survey of obstetricians and gynecologists determined that only 39% administered influenza vaccine to obstetric patients, although 86% agreed that pregnant women's risk for influenza-related morbidity and mortality increases during the last two trimesters (*131*).

Recent data indicate that self-report of influenza vaccination among adults, compared with extraction from the medical record, is both sensitive and specific (*132*). Patient self-reports should be accepted as evidence of influenza vaccination in clinical practice (*132*). However, information on the validity of parents' reports of pediatric influenza vaccination is not yet available.

Recommendations for Using Inactivated and Live, Attenuated Influenza Vaccines

Both the inactivated influenza vaccine and LAIV can be used to reduce the risk for influenza. LAIV is approved for use among healthy persons aged 5–49 years. Inactivated influenza vaccine is approved for persons aged ≥6 months, including those with high-risk conditions (see following sections on inactivated influenza vaccine and live, attenuated influenza vaccine).

Target Groups for Vaccination

Persons at Increased Risk for Complications

Vaccination with inactivated influenza vaccine is recommended for the following persons who are at increased risk for complications from influenza:

- persons aged ≥65 years;
- residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma (hypertension is not considered a high-risk condition);
- adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV]);
- adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise

respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
- children and adolescents (aged 6 months–18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for experiencing Reye syndrome after influenza infection;
- women who will be pregnant during the influenza season; and
- children aged 6–23 months.

In 2004, approximately 88 million persons in the United States were included in one or more of these target groups, including 36 million persons aged ≥65 years, 1.6 million long-term–care facility residents, 6 million children aged 6–23 months, 42 million persons aged 2–64 years with one or more conditions associated with an increased risk for influenza-related complications, and 4 million pregnant women (CDC, National Immunization Program, unpublished data, 2005).

Persons Aged 50–64 Years

Vaccination is recommended for persons aged 50–64 years because this group has an increased prevalence of persons with high-risk conditions. In 2002, approximately 43.6 million persons in the United States were aged 50–64 years, of whom 13.5 million (34%) had one or more high-risk medical conditions (*133*). Influenza vaccine has been recommended for this entire age group to increase the low vaccination rates among persons in this age group with high-risk conditions (see preceding section). Age-based strategies are more successful in increasing vaccine coverage than patient-selection strategies based on medical conditions. Persons aged 50–64 years without high-risk conditions also receive benefit from vaccination in the form of decreased rates of influenza illness, decreased work absenteeism, and decreased need for medical visits and medication, including antibiotics (*9–12*). Furthermore, 50 years is an age when other preventive services begin and when routine assessment of vaccination and other preventive services has been recommended (*134,135*).

Persons Who Can Transmit Influenza to Those at High Risk

Persons who are clinically or subclinically infected can transmit influenza virus to persons at high risk for complications from influenza. Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might reduce influenza-related deaths among persons at high risk. Evidence from two studies indicates that vaccination of health-care workers is associated with decreased deaths among nursing home patients (*125,126*), and hospital-based influenza outbreaks frequently occur where unvaccinated health-care workers are employed. Administration of LAIV has been demonstrated to reduce MAARI in contacts of vaccine recipients (*136*), and to reduce ILI-related economic and medical consequences (such as work days lost and number of health-care provider visits). In addition to health-care workers, additional groups that can transmit influenza to high-risk persons and that should be vaccinated include
- employees of assisted living and other residences for persons in groups at high risk;
- persons who provide home care to persons in groups at high risk; and
- household contacts (including children) of persons in groups at high risk.

In addition, because children aged 0–23 months are at increased risk for influenza-related hospitalization (*54–56*), vaccination is recommended for their household contacts and out-of-home caregivers, particularly for contacts of children aged 0–5 months, because influenza vaccines have not been approved by FDA for use among children aged <6 months (see Healthy Young Children).

Healthy persons aged 5–49 years in these groups who are not contacts of severely immunosuppressed persons (see Live, Attenuated Influenza Vaccine Recommendations) can receive either LAIV or inactivated influenza vaccine. All other persons in this group should receive inactivated influenza vaccine.

Health-Care Workers

All health-care workers should be vaccinated against influenza annually (*128*). Facilities that employ health-care workers are strongly encouraged to provide vaccine to workers by using approaches that maximize vaccination rates. This will protect health-care workers, their patients, and communities, and will improve prevention of influenza-associated disease, patient safety, and will reduce disease burden. Influenza vaccination rates among health-care workers should be regularly measured and reported. Although vaccination rates for health-care workers are typically <40%, with moderate effort, organized campaigns can attain higher rates of vaccination among this population (*127,137*). Currently, seven states have legislation requiring annual influenza vaccination of health-care workers or the signing of an informed declination (*128*), and 15 states have regulations regarding vaccination of health-care workers in long-term–care facilities (*138*). Physicians, nurses, and other workers in both hospital and outpatient-care settings, including medical emergency-response workers (e.g., paramedics and emergency medical technicians), should be vaccinated, as should employees of nursing home and chronic-care facilities who have contact with patients or residents.

Additional Information Regarding Vaccination of Specific Populations

Pregnant Women

Influenza-associated excess deaths among pregnant women were documented during the pandemics of 1918–19 and 1957–58 (*49,139–141*). Case reports and limited studies also indicate that pregnancy can increase the risk for serious medical complications of influenza (*142–146*). An increased risk might result from 1) increases in heart rate, stroke volume, and oxygen consumption; 2) decreases in lung capacity; and 3) changes in immunologic function during pregnancy. A study of the effect of influenza during 17 interpandemic influenza seasons demonstrated that the relative risk for hospitalization for selected cardiorespiratory conditions among pregnant women enrolled in Medicaid increased from 1.4 during weeks 14–20 of gestation to 4.7 during weeks 37–42, in comparison with women who were 1–6 months postpartum (*147*). Women in their third trimester of pregnancy were hospitalized at a rate (i.e., 250/100,000 pregnant women) comparable with that of nonpregnant women who had high-risk medical conditions. Researchers estimate that an average of 1–2 hospitalizations can be prevented for every 1,000 pregnant women vaccinated (*147*).

Because of the increased risk for influenza-related complications, women who will be pregnant during the influenza season should be vaccinated. Vaccination can occur in any trimester. One study of influenza vaccination of approximately 2,000 pregnant women demonstrated no adverse fetal effects associated with influenza vaccine (*148*).

Healthy Young Children

Studies indicate that rates of hospitalization are higher among young children than older children when influenza viruses are in circulation (*53,55,56,149,150*). The increased rates of hospitalization are comparable with rates for other groups considered at high risk for influenza-related complications. However, the interpretation of these findings has been confounded by co-circulation of respiratory syncytial viruses, which are a cause of serious respiratory viral illness among children and which frequently circulate during the same time as influenza viruses (*151–153*). One study assessed rates of influenza-associated hospitalizations among the entire U.S. population during 1979–2001 and calculated an average rate of approximately 108 hospitalizations per 100,000 person-years in children aged <5 years (*46*). Two recent studies have attempted to separate the effects of respiratory syncytial viruses and influenza viruses on rates of hospitalization among children who do not have high-risk conditions (*54,55*). Both studies reported that otherwise healthy children aged <2 years, and possibly children aged 2–4 years, are at increased risk for influenza-related hospitalization compared with older healthy children (Table 1). Among the Tennessee Medicaid population during 1973–1993, healthy children aged 6 months–<3 years had rates of influenza-associated hospitalization comparable with or higher than rates among children aged 3–14 years with high-risk conditions (*54,56*). Another Tennessee study reported a hospitalization rate per year of 3–4/1,000 healthy children aged <2 years for laboratory-confirmed influenza (*33*).

Because children aged 6–23 months are at substantially increased risk for influenza-related hospitalizations, ACIP recommends vaccination of all children in this age group (*154*). ACIP continues to recommend influenza vaccination of persons aged ≥6 months who have high-risk medical conditions.

The current inactivated influenza vaccine is not approved by FDA for use among children aged <6 months, the pediatric group at greatest risk for influenza-related complications (*54*). Vaccinating their household contacts and out-of-home caregivers might decrease the probability of influenza infection among these children.

Beginning in March 2003, the group of children eligible for influenza vaccine coverage under the Vaccines for Children (VFC) program was expanded to include all VFC-eligible children aged 6–23 months and VFC-eligible children aged 2–18 years who are household contacts of children aged 0–23 months (*155*).

Persons Infected with HIV

Limited information is available regarding the frequency and severity of influenza illness or the benefits of influenza vaccination among persons with HIV infection (*156,157*). However, a retrospective study of young and middle-aged women enrolled in Tennessee's Medicaid program determined that the attributable risk for cardiopulmonary hospitalizations among women with HIV infection was higher during influenza seasons than during the peri-influenza periods. The risk for hospitalization was higher for HIV-infected women than for women with other well-recognized high-risk conditions, including chronic heart and lung diseases (*158*). Another study estimated that the risk for influenza-related death was 9.4–14.6/10,000 persons with acquired immunodeficiency syndrome (AIDS) compared with 0.09–0.10/10,000 among all persons aged 25–54 years and 6.4–7.0/10,000 among persons aged ≥65 years (*159*). Other reports indicate that influenza symptoms might be prolonged and the risk for complications from influenza increased for certain HIV-infected persons (*160–162*).

Inactivated influenza vaccination has been demonstrated to produce substantial antibody titers against influenza among

vaccinated HIV-infected persons who have minimal AIDS-related symptoms and high CD4+ T-lymphocyte cell counts (*163–166*). A limited, randomized, placebo-controlled trial determined that inactivated influenza vaccine was highly effective in preventing symptomatic, laboratory-confirmed influenza infection among HIV-infected persons with a mean of 400 CD4+ T-lymphocyte cells/mm3; a limited number of persons with CD4+ T-lymphocyte cell counts of <200 were included in that study (*167*). A nonrandomized study among HIV-infected persons determined that influenza vaccination was most effective among persons with >100 CD4+ cells and among those with <30,000 viral copies of HIV type-1/mL (*162*). Among persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, inactivated influenza vaccine might not induce protective antibody titers (*165,166*); a second dose of vaccine does not improve the immune response in these persons (*166,167*).

One study determined that HIV RNA (ribonucleic acid) levels increased transiently in one HIV-infected person after influenza infection (*168*). Studies have demonstrated a transient (i.e., 2–4 week) increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration (*165,169*). Other studies using similar laboratory techniques have not documented a substantial increase in the replication of HIV (*170–173*). Deterioration of CD4+ T-lymphocyte cell counts or progression of HIV disease have not been demonstrated among HIV-infected persons after influenza vaccination compared with unvaccinated persons (*166,174*). Limited information is available concerning the effect of antiretroviral therapy on increases in HIV RNA levels after either natural influenza infection or influenza vaccination (*156,175*). Because influenza can result in serious illness and because vaccination with inactivated influenza vaccine can result in the production of protective antibody titers, vaccination will benefit HIV-infected persons, including HIV-infected pregnant women.

Breastfeeding Mothers

Influenza vaccine is safe for mothers who are breastfeeding and their infants. Breastfeeding does not adversely affect the immune response and is not a contraindication for vaccination.

Travelers

The risk for exposure to influenza during travel depends on the time of year and destination. In the tropics, influenza can occur throughout the year. In the temperate regions of the Southern Hemisphere, the majority of influenza activity occurs during April–September. In temperate climate zones of the Northern and Southern Hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling as part of large organized tourist groups (e.g., on cruise ships) that include persons from areas of the world where influenza viruses are circulating (*176,177*). Persons at high risk for complications of influenza who were not vaccinated with influenza vaccine during the preceding fall or winter should consider receiving influenza vaccine before travel if they plan to

- travel to the tropics,
- travel with organized tourist groups at any time of year, or
- travel to the Southern Hemisphere during April–September.

No information is available regarding the benefits of revaccinating persons before summer travel who were already vaccinated in the preceding fall. Persons at high risk who receive the previous season's vaccine before travel should be revaccinated with the current vaccine the following fall or winter. Persons aged ≥50 years and persons at high risk should consult with their physicians before embarking on travel during the summer to discuss the symptoms and risks for influenza and the advisability of carrying antiviral medications for either prophylaxis or treatment of influenza.

General Population

In addition to the groups for which annual influenza vaccination is recommended, physicians should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected (the vaccine can be administered to children aged ≥6 months), depending on vaccine availability (see Influenza Vaccine Supply). Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students or other persons in institutional settings (e.g., those who reside in dormitories) should be encouraged to receive vaccine to minimize the disruption of routine activities during epidemics.

Comparison of LAIV with Inactivated Influenza Vaccine

Both inactivated influenza vaccine and LAIV are available to reduce the risk for influenza infection and illness. However, the vaccines also differ in key ways (Table 3).

Major Similarities

LAIV and inactivated influenza vaccine contain strains of influenza viruses that are antigenically equivalent to the annually recommended strains: one influenza A (H3N2) virus, one A (H1N1) virus, and one B virus. Each year, one or more

TABLE 3. Live, attenuated influenza vaccine (LAIV) compared with inactivated influenza vaccine

Factor	LAIV	Inactivated influenza vaccine
Route of administration	Intranasal spray	Intramuscular injection
Type of vaccine	Live virus	Killed virus
No. of included virus strains	3 (2 influenza A, 1 influenza B)	Same as LAIV
Vaccine virus strains updated	Annually	Same as LAIV
Frequency of administration	Annually	Same as LAIV
Approved age and risk groups*	Healthy persons aged 5–49 yrs	Persons aged ≥6 mos
Can be administered to family members or close contacts of immunosuppressed persons not requiring a protected environment	Yes	Yes
Can be administered to family members or close contacts of immunosuppressed persons requiring a protected environment (e.g., hematopoietic stemcell transplant recipient)	Inactivated influenza vaccine preferred	Yes
Can be administered to family members or close contacts of persons at high risk but not severely immunosuppressed	Yes	Yes
Can be simultaneously administered with other vaccines	Yes†	Yes§
If not simultaneously administered, can be administered within 4 weeks of another live vaccine	Prudent to space 4 weeks apart	Yes
If not simultaneously administered, can be administered within 4 weeks of an inactivated vaccine	Yes	Yes

* Populations at high risk from complications of influenza infection include persons aged ≥65 years; residents of nursing homes and other chronic-care facilities that house persons with chronic medical conditions; adults and children with chronic disorders of the pulmonary or cardiovascular systems; adults and children with chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunnosuppression; children and adolescents receiving long-term aspirin therapy (at risk for developing Reye syndrome after wild-type influenza infection); pregnant women; and children aged 6–23 months.
† No data are available regarding effect on safety or efficacy.
§ Inactivated influenza vaccine coadministration has been evaluated systematically only among adults with pneumococcal polysaccharide vaccine.

virus strains might be changed on the basis of global surveillance for influenza viruses and the emergence and spread of new strains. Viruses for both vaccines are grown in eggs. Both vaccines are administered annually to provide optimal protection against influenza infection (Table 3).

Major Differences

Inactivated influenza vaccine contains killed viruses, whereas LAIV contains live, attenuated viruses still capable of replication. LAIV is administered intranasally by sprayer, whereas inactivated influenza vaccine is administered intramuscularly by injection. LAIV is more expensive than inactivated influenza vaccine, although the price differential between inactivated vaccine and LAIV has decreased for the 2005–06 season. LAIV is approved for use among healthy persons aged 5–49 years; inactivated influenza vaccine is approved for use among persons aged ≥6 months, including those who are healthy and those with chronic medical conditions (Table 3).

Inactivated Influenza Vaccine Recommendations

Persons Who Should Not Be Vaccinated with Inactivated Influenza Vaccine

Inactivated influenza vaccine should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine without first consulting a physician (see Side Effects and Adverse Reactions). Prophylactic use of antiviral agents is an option for preventing influenza among such persons. However, persons who have a history of anaphylactic hypersensitivity to vaccine components but who are also at high risk for complications from influenza can benefit from vaccine after appropriate allergy evaluation and desensitization. Information regarding vaccine components is located in package inserts from each manufacturer. Persons with acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever do not contraindicate use of influenza vaccine, particularly among children with mild upper-respiratory-tract infection or allergic rhinitis.

Dosage

Dosage recommendations vary according to age group (Table 4). Among previously unvaccinated children aged <9 years, 2 doses administered ≥1 month apart are recommended for satisfactory antibody responses. If possible, the second dose should be administered before December. If a child aged <9 years receiving vaccine for the first time does not receive a second dose of vaccine within the same season, only 1 dose of vaccine should be administered the following season. Two doses are not required at that time. Among adults, studies have indicated limited or no improvement in antibody response when a second dose is administered during the same season (*178–180*). Even when the current influenza vaccine contains one or more antigens administered in previous years, annual vaccination with the current vaccine is necessary because immunity declines during the year after vaccination (*181,182*). Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season. Because of lack of vaccine efficacy data, ACIP does not recommend that a child receiving influenza vaccine for the first time be given the first dose of vaccine in the spring, followed by the second dose in the autumn of the same year.

Route

The intramuscular route is recommended for influenza vaccine. Adults and older children should be vaccinated in the deltoid muscle. A needle length ≥1 inch can be considered for these age groups because needles <1 inch might be of insufficient length to penetrate muscle tissue in certain adults and older children (*183*).

Infants and young children should be vaccinated in the anterolateral aspect of the thigh (*67*). ACIP recommends a needle length of 7/8–1 inch for children aged <12 months for intramuscular vaccination into the anterolateral thigh. When injecting into the deltoid muscle among children with adequate deltoid muscle mass, a needle length of 7/8–1.25 inches is recommended (*67*).

TABLE 4. Inactivated influenza vaccine* dosage, by age group — United States, 2005–06 season

Age group†	Dose	No. of doses	Route§
6–35 mos	0.25 mL	1 or 2¶	Intramuscular
3–8 yrs	0.50 mL	1 or 2¶	Intramuscular
≥9 yrs	0.50 mL	1	Intramuscular

* A 0.5-mL dose contains 15 mg each of A/California/7/2004 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Shanghai/361/2002-like antigens. For the A/California/7/2004 (H3N2)-like antigen, manufacturers may use the antigenically equivalent A/New York/55/2004 virus, and for the B/Shanghai/361/2002-like antigen, manufacturers may use the antigenically equivalent B/Jilin/20/2003 virus or B/Jiangsu/10/2003 virus. Manufacturers include Sanofi Pasteur, Inc. (formerly Aventis Pasteur, Inc.) (FluZone® split virus); and Chiron (Fluvirin™ purified-surface-antigen vaccine). FluZone is approved by the Food and Drug Administration for use among persons aged ≥6 months. Fluvirin is approved for use in persons aged ≥4 years. For further product information, call Sanofi Pasteur at 800-822-2463 or Chiron at 800-244-7668.

† Because of their decreased potential for causing febrile reactions, only split-virus vaccines should be used for children aged <13 years. Whole-virus vaccine is not available in the United States. Split-virus vaccine might be labeled as *split*, *subvirion*, or *purified-surface-antigen* vaccine. Immunogenicity and side effects of split- and whole-virus vaccines are similar among adults when vaccines are administered at the recommended dosage.

§ For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.

¶ Two doses administered at least 1 month apart are recommended for children aged <9 years who are receiving influenza vaccine for the first time.

Side Effects and Adverse Reactions

When educating patients regarding potential side effects, clinicians should emphasize that 1) inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza; and 2) coincidental respiratory disease unrelated to influenza vaccination can occur after vaccination.

Local Reactions

In placebo-controlled studies among adults, the most frequent side effect of vaccination is soreness at the vaccination site (affecting 10%–64% of patients) that lasts <2 days (*12,184–186*). These local reactions typically are mild and rarely interfere with the person's ability to conduct usual daily activities. One blinded, randomized, cross-over study among 1,952 adults and children with asthma, demonstrated that only body aches were reported more frequently after inactivated influenza vaccine (25.1%) than placebo-injection (20.8%) (*187*). One study (*83*) reported 20%–28% of children with asthma aged 9 months–18 years with local pain and swelling, and another study (*80*) reported 23% of children aged 6 months–4 years with chronic heart or lung disease had local reactions. A different study (*81*) reported no difference in local reactions among 53 children aged 6 months–6 years with high-risk medical conditions or among 305 healthy children aged 3–12 years in a placebo-controlled trial of inactivated influenza vaccine. In a study of 12 children aged 5–32 months, no substantial local or systemic reactions were noted (*188*).

Systemic Reactions

Fever, malaise, myalgia, and other systemic symptoms can occur after vaccination with inactivated vaccine and most often affect persons who have had no previous exposure to the influenza virus antigens in the vaccine (e.g., young children) (*189,190*). These reactions begin 6–12 hours after vaccination and can persist for 1–2 days. Recent placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of split-virus influenza vaccine is not

associated with higher rates of systemic symptoms (e.g., fever, malaise, myalgia, and headache) when compared with placebo injections (*12,184–186*).

Less information from published studies is available for children, compared with adults. However, in a randomized crossover study among both children and adults with asthma, no increase in asthma exacerbations was reported for either age group (*187*). An analysis of 215,600 children aged <18 years and 8,476 children aged 6–23 months enrolled in one of five health maintenance organizations reported no increase in biologically plausible medically attended events during the 2 weeks after inactivated influenza vaccination, compared with control periods 3–4 weeks before and after vaccination (*191*). In a study of 791 healthy children (*71*), postvaccination fever was noted among 11.5% of children aged 1–5 years, 4.6% among children aged 6–10 years, and 5.1% among children aged 11–15 years. Among children with high-risk medical conditions, one study of 52 children aged 6 months–4 years reported fever among 27% and irritability and insomnia among 25% (*80*); and a study among 33 children aged 6–18 months reported that one child had irritability and one had a fever and seizure after vaccination (*192*). No placebo comparison was made in these studies. However, in pediatric trials of A/New Jersey/76 swine influenza vaccine, no difference was reported between placebo and split-virus vaccine groups in febrile reactions after injection, although the vaccine was associated with mild local tenderness or erythema (*81*).

Limited data regarding potential adverse events after influenza vaccination are available from the Vaccine Adverse Event Reporting System (VAERS). During January 1, 1991–June 30, 2004, VAERS received 1,895 reports of adverse events among children aged <18 years, including 479 reports of adverse events among children aged 6–23 months. The number of influenza vaccine doses received by children during this entire period is unknown (CDC, unpublished data, 2005). A recently published review of VAERS reports of trivalent inactivated influenza vaccine (TIV) in children aged 6–23 months documented that the most frequently reported adverse events were fever, rash, injection-site reactions, and seizures. The majority of the small total number of reported seizures appeared to be febrile (*193*). Because of the limitations of passive reporting systems, determining causality for specific types of adverse events, with the exception of injection-site reactions, is usually not possible by using VAERS data alone. A population-based study of TIV safety in children aged 6–23 months indicated no vaccine associated adverse events that had a plausible relationship to vaccination (*194*).

Health-care professionals should promptly report to VAERS all clinically significant adverse events after influenza vaccination of children, even if the health-care professional is not certain that the vaccine caused the event. The Institute of Medicine has specifically recommended reporting of potential neurologic complications (e.g., demyelinating disorders such as Guillain-Barré syndrome [GBS]), although no evidence exists of a causal relationship between influenza vaccine and neurologic disorders in children.

Immediate — presumably allergic — reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination (*195*). These reactions probably result from hypersensitivity to certain vaccine components; the majority of reactions probably are caused by residual egg protein. Although current influenza vaccines contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Persons who have had hives or swelling of the lips or tongue, or who have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who have documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs, including those who have had occupational asthma or other allergic responses to egg protein, might also be at increased risk for allergic reactions to influenza vaccine, and consultation with a physician should be considered. Protocols have been published for safely administering influenza vaccine to persons with egg allergies (*196–198*).

Hypersensitivity reactions to any vaccine component can occur. Although exposure to vaccines containing thimerosal can lead to induction of hypersensitivity, the majority of patients do not have reactions to thimerosal when it is administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity (*199,200*). When reported, hypersensitivity to thimerosal usually has consisted of local, delayed hypersensitivity reactions (*199*).

Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an increased frequency of GBS (*201,202*). Among persons who received the swine influenza vaccine in 1976, the rate of GBS was <10 cases/1 million persons vaccinated. The risk for influenza vaccine-associated GBS is higher among persons aged ≥25 years than persons <25 years (*201*). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. Obtaining strong epidemiologic evidence for a possible limited increase in risk is difficult for such a rare condition as GBS, which has an annual incidence of 10–20 cases/1 million adults (*203*). More definitive data probably will require using other methodologies (e.g., laboratory studies of the pathophysiology of GBS).

During three of four influenza seasons studied during 1977–1991, the overall relative risk estimates for GBS after influenza vaccination were slightly elevated but were not statistically significant in any of these studies (*204–206*). However, in a study of the 1992–93 and 1993–94 seasons, the overall relative risk for GBS was 1.7 (95% CI = 1.0–2.8; p = 0.04) during the 6 weeks after vaccination, representing approximately 1 additional case of GBS/1 million persons vaccinated. The combined number of GBS cases peaked 2 weeks after vaccination (*207*). Thus, investigations to date have not documented a substantial increase in GBS associated with influenza vaccines (other than the swine influenza vaccine in 1976), and that, if influenza vaccine does pose a risk, it is probably slightly more than one additional case/1 million persons vaccinated. Recent data from VAERS has documented decreased reporting of post influenza vaccine GBS across age groups, despite overall increased reporting for influenza vaccine (*208*). Cases of GBS after influenza infection have been reported, but no epidemiologic studies have documented such an association (*209,210*). Substantial evidence exists that multiple infectious illnesses, most notably *Campylobacter jejuni*, and upper respiratory tract infections are associated with GBS (*203,211–213*).

Even if GBS were a true side effect of vaccination in the years after 1976, the estimated risk for GBS of approximately 1 additional case/1 million persons vaccinated is substantially less than the risk for severe influenza, which can be prevented by vaccination among all age groups, especially persons aged ≥65 years and those who have medical indications for influenza vaccination (Table 1) (see Hospitalizations and Deaths from Influenza). The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death substantially outweigh the possible risks for experiencing vaccine-associated GBS. The average case fatality ratio for GBS is 6% and increases with age (*203,214*). No evidence indicates that the case fatality ratio for GBS differs among vaccinated persons and those not vaccinated.

The incidence of GBS among the general population is low, but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history (*204,215*). Thus, the likelihood of coincidentally experiencing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of GBS is unknown; therefore, avoiding vaccinating persons who are not at high risk for severe influenza complications and who are known to have experienced GBS within 6 weeks after a previous influenza vaccination is prudent. As an alternative, physicians might consider using influenza antiviral chemoprophylaxis for these persons. Although data are limited, for the majority of persons who have a history of GBS and who are at high risk for severe complications from influenza, the established benefits of influenza vaccination justify yearly vaccination.

Live, Attenuated Influenza Vaccine Recommendations

Background

Description and Action Mechanisms. LAIVs have been in development since the 1960s in the United States, where they have been evaluated as mono-, bi-, and trivalent formulations (*216–218*). The LAIV licensed for use in the United States beginning in 2003 is produced by MedImmune, Inc. (Gaithersburg, Maryland; http://www.medimmune.com) and marketed under the name FluMist™. It is a live, trivalent, intranasally administered vaccine that is

- attenuated, producing mild or no signs or symptoms related to influenza virus infection;
- temperature-sensitive, a property that limits the replication of the vaccine viruses at 38°C–39°C, and thus restricts LAIV viruses from replicating efficiently in human lower airways; and
- cold-adapted, replicating efficiently at 25°C, a temperature that is permissive for replication of LAIV viruses, but restrictive for replication of different wild-type viruses.

In animal studies, LAIV viruses replicate in the mucosa of the nasopharynx, inducing protective immunity against viruses included in the vaccine, but replicate inefficiently in the lower airways or lungs.

The first step in developing an LAIV was the derivation of two stably attenuated master donor viruses (MDV), one for type A and one for type B influenza viruses. The two MDVs each acquired the cold-adapted, temperature-sensitive, attenuated phenotypes through serial passage in viral culture conducted at progressively lower temperatures. The vaccine viruses in LAIV are reassortant viruses containing genes from these MDVs that confer attenuation, temperature sensitivity, and cold adaptation and genes from the recommended contemporary wild-type influenza viruses, encoding the surface antigens hemagglutinin (HA) and neuraminidase (NA). Thus, MDVs provide the stably attenuated vehicles for presenting influenza HA and NA antigens, to which the protective antibody response is directed, to the immune system. The reassortant vaccine viruses are grown in embryonated hens eggs. After the vaccine is formulated and inserted into individual sprayers for nasal administration, the vaccine must be stored at –15°C or colder.

The immunogenicity of the approved LAIV has been assessed in multiple studies (*102,219–224*), which included approximately 100 children aged 5–17 years, and approximately 300 adults aged 18–49 years. LAIV virus strains replicate primarily in nasopharyngeal epithelial cells. The protective mechanisms induced by vaccination with LAIV are not completely understood but appear to involve both serum and nasal secretory antibodies. No single laboratory measurement closely correlates with protective immunity induced by LAIV.

Shedding and Transmission of Vaccine Viruses. Available data indicate that both children and adults vaccinated with LAIV can shed vaccine viruses for ≥2 days after vaccination, although in lower titers than typically occur with shedding of wild-type influenza viruses. Shedding should not be equated with person-to-person transmission of vaccine viruses, although, in rare instances, shed vaccine viruses can be transmitted from vaccinees to nonvaccinated persons.

One unpublished study in a child care center setting–assessed transmissibility of vaccine viruses from 98 vaccinated to 99 unvaccinated subjects, all aged 8–36 months. Eighty percent of vaccine recipients shed one or more virus strains, with a mean of 7.6 days' duration (*225*). One vaccine type influenza type B isolate was recovered from a placebo recipient and was confirmed to be vaccine-type virus. The type B isolate retained the cold-adapted, temperature-sensitive, attenuated phenotype, and it possessed the same genetic sequence as a virus shed from a vaccine recipient in the same children's play group. The placebo recipient from whom the influenza type B vaccine virus was isolated did not exhibit symptoms that were different from those experienced by vaccine recipients. The estimated probability of acquiring vaccine virus after close contact with a single LAIV recipient in this child care population was 0.58%–2.4%.

One study assessing shedding of vaccine viruses in 20 healthy vaccinated adults aged 18–49 years demonstrated that the majority of shedding occurred within the first 3 days after vaccination, although one subject was noted to shed virus on day 7 after vaccine receipt. No subject shed vaccine viruses ≥10 days after vaccination. Duration or type of symptoms associated with receipt of LAIV did not correlate with duration of shedding of vaccine viruses. Person-to-person transmission of vaccine viruses was not assessed in this study (*226*).

Another study assessing shedding of vaccine viruses in 14 healthy adults aged 18–49 years indicated that 50% of these adults had viral antigen detected by direct immunofluorescence or rapid antigen tests within 7 days of vaccination. Most viral shedding was detected on day 2 or 3. Person-to-person transmission of vaccine viruses was not assessed in this study (*227*).

Stability of Vaccine Viruses. In clinical trials, viruses shed by vaccine recipients have been phenotypically stable. In one study, nasal and throat swab specimens were collected from 17 study participants for 2 weeks after vaccine receipt (*228*). Virus isolates were analyzed by multiple genetic techniques. All isolates retained the LAIV genotype after replication in the human host, and all retained the cold-adapted and temperature-sensitive phenotypes.

Using LAIV

LAIV is an option for vaccination of healthy persons aged 5–49 years, including health-care workers and other persons in close contact with groups at high risk and those wanting to avoid influenza. During periods when inactivated vaccine is in short supply, use of LAIV is encouraged when feasible for eligible persons (including health-care workers) because use of LAIV by these persons might increase availability of inactivated vaccine for persons in groups at high risk. Possible advantages of LAIV include its potential to induce a broad mucosal and systemic immune response, its ease of administration, and the acceptability of an intranasal rather than intramuscular route of administration.

Persons Who Should Not Be Vaccinated with LAIV

The following populations should not be vaccinated with LAIV:

- persons aged <5 years or those aged ≥50 years;*
- persons with asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; persons with other underlying medical conditions, including such metabolic diseases as diabetes, renal dysfunction, and hemoglobinopathies; or persons with known or suspected immunodeficiency diseases or who are receiving immunosuppressive therapies;*
- children or adolescents receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza infection);*
- persons with a history of GBS;
- pregnant women;* or
- persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs.

Close Contacts of Persons at High Risk for Complications from Influenza

Close contacts of persons at high risk for complications from influenza should receive influenza vaccine to reduce transmission of wild-type influenza viruses to persons at high risk.

* These persons should receive inactivated influenza vaccine.

ACIP has not indicated a preference for inactivated influenza vaccine use by health-care workers or other persons who have close contact with persons with lesser degrees of immunosuppression (e.g., persons with diabetes, persons with asthma taking corticosteroids, or persons infected with HIV) or for inactivated influenza vaccine use by health-care workers or other healthy persons aged 5–49 years in close contact with all other groups at high risk. Use of inactivated influenza vaccine is preferred for vaccinating household members, health-care workers, and others who have close contact with severely immunosuppressed persons (e.g., patients with hematopoietic stem cell transplants) during those periods in which the immunosuppressed person requires care in a protective environment. The rationale for not using LAIV among health-care workers caring for such patients is the theoretical risk that a live, attenuated vaccine virus could be transmitted to the severely immunosuppressed person. If a health-care worker receives LAIV, that worker should refrain from contact with severely immunosuppressed patients for 7 days after vaccine receipt. Hospital visitors who have received LAIV should refrain from contact with severely immunosuppressed persons for 7 days after vaccination; however, such persons need not be excluded from visitation of patients who are not severely immunosuppressed.

Personnel Who May Administer LAIV

Low-level introduction of vaccine viruses into the environment is likely unavoidable when administering LAIV. The risk for acquiring vaccine viruses from the environment is unknown but likely to be limited. Severely immunosuppressed persons should not administer LAIV. However, other persons at high risk for influenza complications may administer LAIV. These include persons with underlying medical conditions placing them at high risk or who are likely to be at risk, including pregnant women, persons with asthma, and persons aged ≥50 years.

LAIV Dosage and Administration

LAIV is intended for intranasal administration only and should not be administered by the intramuscular, intradermal, or intravenous route. LAIV must be thawed before administration. This can be accomplished by holding an individual sprayer in the palm of the hand until thawed, with subsequent immediate administration. Alternatively, the vaccine can be thawed in a refrigerator and stored at 2°C–8°C for ≤24 hours before use. Vaccine should not be refrozen after thawing. LAIV is supplied in a prefilled single-use sprayer containing 0.5 mL of vaccine. Approximately 0.25 mL (i.e., half of the total sprayer contents) is sprayed into the first nostril while the recipient is in the upright position. An attached dose-divider clip is removed from the sprayer to administer the second half of the dose into the other nostril. If the vaccine recipient sneezes after administration, the dose should not be repeated.

LAIV should be administered annually according to the following schedule:

- Children aged 5–8 years previously unvaccinated at any time with either LAIV or inactivated influenza vaccine should receive 2 doses[†] of LAIV separated by 6–10 weeks.
- Children aged 5–8 years previously vaccinated at any time with either LAIV or inactivated influenza vaccine should receive 1 dose of LAIV. They do not require a second dose.
- Persons aged 9–49 years should receive 1 dose of LAIV.

LAIV can be administered to persons with minor acute illnesses (e.g., diarrhea or mild upper respiratory tract infection with or without fever). However, if clinical judgment indicates nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness.

Whether concurrent administration of LAIV with other vaccines affects the safety or efficacy of either LAIV or the simultaneously administered vaccine is unknown. In the absence of specific data indicating interference, following the ACIP general recommendations for immunization is prudent (*67*). Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines. An inactivated vaccine can be administered either simultaneously or at any time before or after LAIV. Two live vaccines not administered on the same day should be administered ≥4 weeks apart when possible.

LAIV and Use of Influenza Antiviral Medications

The effect on safety and efficacy of LAIV coadministration with influenza antiviral medications has not been studied. However, because influenza antivirals reduce replication of influenza viruses, LAIV should not be administered until 48 hours after cessation of influenza antiviral therapy, and influenza antiviral medications should not be administered for 2 weeks after receipt of LAIV.

LAIV Storage

LAIV must be stored at –15°C or colder. A manufacturer-supplied freezer box was formerly required for storage of LAIV in a frost-free freezer; however, the freezer box is now optional, and LAIV may now be stored in frost-free freezers without

[†] One dose equals 0.5 mL, divided equally between each nostril.

using a freezer box. LAIV can be thawed in a refrigerator and stored at 2°C–8°C for ≤60 hours before use. It should not be refrozen after thawing.

Side Effects and Adverse Reactions

Twenty prelicensure clinical trials assessed the safety of the approved LAIV. In these combined studies, approximately 28,000 doses of the vaccine were administered to approximately 20,000 subjects. A subset of these trials were randomized, placebo-controlled studies in which an estimated 4,000 healthy children aged 5–17 years and 2,000 healthy adults aged 18–49 years were vaccinated. The incidence of adverse events possibly complicating influenza (e.g., pneumonia, bronchitis, bronchiolitis, or central nervous system events) was not statistically different among LAIV and placebo recipients aged 5–49 years. LAIV is made from attenuated viruses and does not cause influenza in vaccine recipients.

Children. In a subset of healthy children aged 60–71 months from one clinical trial (*97,98*), certain signs and symptoms were reported more often among LAIV recipients after the first dose (n = 214) than placebo recipients (n = 95) (e.g., runny nose, 48.1% versus 44.2%; headache, 17.8% versus 11.6%; vomiting, 4.7% versus 3.2%; and myalgias, 6.1% versus 4.2%), but these differences were not statistically significant. In other trials, signs and symptoms reported after LAIV administration have included runny nose or nasal congestion (20%–75%), headache (2%–46%), fever (0%–26%), vomiting (3%–13%), abdominal pain (2%), and myalgias (0%–21%) (*219,222,224,229–231*). These symptoms were associated more often with the first dose and were self-limited. Unpublished data from a study including subjects aged 1–17 years indicated an increase in asthma or reactive airways disease in the subset aged 12–59 months. Because of this, LAIV is not approved for use among children aged <60 months.

Adults. Among adults, runny nose or nasal congestion (28%–78%), headache (16%–44%), and sore throat (15%–27%) have been reported more often among vaccine recipients than placebo recipients (*100,232,233*). In one clinical trial (*100*) among a subset of healthy adults aged 18–49 years, signs and symptoms reported more frequently among LAIV recipients (n = 2,548) than placebo recipients (n = 1,290) within 7 days after each dose included cough (13.9% versus 10.8%); runny nose (44.5% versus 27.1%); sore throat (27.8% versus 17.1%); chills (8.6% versus 6.0%); and tiredness/weakness (25.7% versus 21.6%).

Safety Among Groups at High Risk from Influenza-Related Morbidity. Until additional data are acquired and analyzed, persons at high risk for experiencing complications from influenza infection (e.g., immunocompromised patients; patients with asthma, cystic fibrosis, or chronic obstructive pulmonary disease; or persons aged ≥65 years) should not be vaccinated with LAIV. Protection from influenza among these groups should be accomplished by using inactivated influenza vaccine.

Serious Adverse Events. Serious adverse events among healthy children aged 5–17 years or healthy adults aged 18–49 years occurred at a rate of <1%. Surveillance should continue for adverse events that might not have been detected in previous studies. A preliminary review of reports to VAERS after distribution of approximately 800,000 doses during the 2003–04 influenza season did not reveal any substantial new safety concerns (*234*). Health-care professionals should promptly report all clinically significant adverse events after LAIV administration to VAERS, as recommended for inactivated influenza vaccine.

Recommended Vaccines for Different Age Groups

When vaccinating children aged 6 months–3 years, health-care providers should use inactivated influenza vaccine that has been approved by FDA for this age group. Inactivated influenza vaccine from Sanofi Pasteur, Inc., (FluZone split-virus) is approved for use among persons aged ≥6 months. Inactivated influenza vaccine from Chiron (Fluvirin) is labeled in the United States for use among persons aged ≥4 years because data to demonstrate efficacy among younger persons have not been provided to FDA. Live, attenuated influenza vaccine from MedImmune (FluMist) is approved for use by healthy persons aged 5–49 years (Table 5).

Timing of Annual Influenza Vaccination

The annual supply of influenza vaccine and the timing of its distribution cannot be guaranteed in any year. Information regarding the supply of 2005–06 vaccine might not be available until late summer or early fall 2005. To allow vaccine providers to plan for the upcoming vaccination season, taking into account the yearly possibility of vaccine delays or shortages and the need to ensure vaccination of persons at high risk and their contacts, ACIP recommends that inactivated influenza vaccine campaigns conducted in October focus primarily on persons at increased risk for influenza complications and their contacts, including health-care workers. Campaigns conducted in November and later should continue to vaccinate persons at high risk and their contacts, but also vaccinate other persons who wish to decrease their risk for influenza infection. Vaccination for all groups should continue into December and beyond. CDC and other public health agencies will assess the vaccine supply on a continuing

TABLE 5. Approved influenza vaccines for different age groups — United States

Vaccine	6 mos–3 yrs	4 yrs	5–49 yrs	≥50 yrs
FluZone® (Sanofi Pasteur, Inc.)	X*	X	X	X
Fluvirin™ (Chiron)		X	X	X
FluMist™ (MedImmune, Inc.)			X	

* Children aged 6–35 months should receive 0.25 mL/dose. Persons aged >35 months should receive 0.50 mL/dose.

basis throughout the manufacturing period and will make recommendations preceding the 2005–06 influenza season regarding the need for tiered timing of inactivated influenza vaccination of different risk groups. Because LAIV is approved for use in healthy persons 5–49 years, its use has not been subject to tiered timing.

Vaccination Before October

To avoid missed opportunities for vaccination of persons at high risk for serious complications, such persons should be offered vaccine beginning in September during routine health-care visits or during hospitalizations, if vaccine is available. In facilities housing older persons (e.g., nursing homes), vaccination before October typically should be avoided because antibody levels in such persons can begin to decline within a limited time after vaccination (*235*). In addition, children aged <9 years who have not been previously vaccinated and who need 2 doses before the start of the influenza season can receive their first dose in September so that both doses of the most up-to-date vaccine can be administered before the onset of influenza activity. For previously vaccinated children, 2 doses are needed to provide optimal protection against influenza.

Vaccination in October and November

The optimal time to vaccinate is usually during October–November. ACIP recommends that vaccine providers focus their vaccination efforts in October and earlier primarily on persons aged ≥50 years, persons aged <50 years at increased risk for influenza-related complications (including children aged 6–23 months), household contacts of persons at high risk (including out-of-home caregivers and household contacts of children aged 0–23 months), and health-care workers. Vaccination of children aged <9 years who are receiving vaccine for the first time should also begin in October or earlier because those persons need a booster dose 1 month after the initial dose. Efforts to vaccinate other persons who wish to decrease their risk for influenza infection should begin in November; however, if such persons request vaccination in October, vaccination should not be deferred, unless vaccine supplies dictate otherwise. Materials to assist providers in prioritizing early vaccine are available at http://www.cdc.gov/flu/professionals/vaccination/index.htm (see also Travelers in this report).

Timing of Organized Vaccination Campaigns

Persons and institutions planning substantial organized vaccination campaigns should consider scheduling these events after mid-October because the availability of vaccine in any location cannot be ensured consistently in early fall. Scheduling campaigns after mid-October will minimize the need for cancellations because vaccine is unavailable. Campaigns conducted before November using inactivated vaccine should focus efforts on vaccination of persons aged ≥50 years, persons aged <50 years at increased risk for influenza-related complications (including children aged 6–23 months and pregnant women), health-care workers, and household contacts of persons at high-risk (including children aged 0–23 months) to the extent feasible. Campaigns using the LAIV are also optimally conducted in October and November.

Vaccination in December and Later

After November, many persons who should or want to receive influenza vaccine remain unvaccinated. In addition, substantial amounts of vaccine are often left over at the end of the influenza season. To improve vaccine coverage, influenza vaccine should continue to be offered in December and throughout the influenza season as long as vaccine supplies are available, even after influenza activity has been documented in the community. In the United States, seasonal influenza activity can begin to increase as early as October or November, but influenza activity has not reached peak levels in the majority of recent seasons until late December–early March (Table 6). Therefore, although the timing of influenza activity can vary by region, vaccine administered after November

TABLE 6. Month of peak influenza activity* during 29 influenza seasons — United States, 1976–2005

	Month						
	Nov	Dec	Jan	Feb	Mar	Apr	May
No. (%) of years with peak influenza activity	1 (3)	4 (14)	6 (21)	13 (45)	3 (10)	1 (3)	1 (3)

* The peak week of activity was defined as the week with the greatest percentage of respiratory specimens testing positive for influenza on the basis of a 3-week moving average. Laboratory data were provided by U.S. World Health Organization Collaborating Centers (CDC, National Center for Infectious Diseases, unpublished data, 1976–2005).

is likely to be beneficial in the majority of influenza seasons. Adults develop peak antibody protection against influenza infection 2 weeks after vaccination (*236,237*).

Strategies for Implementing Vaccination Recommendations in Health-Care Settings

Successful vaccination programs combine publicity and education for health-care workers and other potential vaccine recipients, a plan for identifying persons at high risk, use of reminder/recall systems, assessment of practice-level vaccination rates with feedback to staff, and efforts to remove administrative and financial barriers that prevent persons from receiving the vaccine, including use of standing orders programs (*19,238*). Using standing orders programs is recommended for long-term–care facilities (e.g., nursing homes and skilled nursing facilities), hospitals, and home health agencies to ensure the administration of recommended vaccinations for adults (*239*). Standing orders programs for both influenza and pneumococcal vaccination should be conducted under the supervision of a licensed practitioner according to a physician-approved facility or agency policy by health-care workers trained to screen patients for contraindications to vaccination, administer vaccine, and monitor for adverse events. The Centers for Medicare and Medicaid Services (CMS) has removed the physician signature requirement for the administration of influenza and pneumococcal vaccines to Medicare and Medicaid patients in hospitals, long-term–care facilities, and home health agencies (*239*). To the extent allowed by local and state law, these facilities and agencies may implement standing orders for influenza and pneumococcal vaccination of Medicare- and Medicaid-eligible patients. Other settings (e.g., outpatient facilities, managed care organizations, assisted living facilities, correctional facilities, pharmacies, and adult workplaces) are encouraged to introduce standing orders programs as well (*20*). In addition, physician reminders (e.g., flagging charts) and patient reminders are recommended strategies for increasing rates of influenza vaccination. Persons for whom influenza vaccine is recommended can be identified and vaccinated in the settings described in the following sections.

Outpatient Facilities Providing Ongoing Care

Staff in facilities providing ongoing medical care (e.g., physicians' offices, public health clinics, employee health clinics, hemodialysis centers, hospital specialty-care clinics, and outpatient rehabilitation programs) should identify and label the medical records of patients who should receive vaccination. Vaccine should be offered during visits beginning in September and throughout the influenza season. The offer of vaccination and its receipt or refusal should be documented in the medical record. Patients for whom vaccination is recommended and who do not have regularly scheduled visits during the fall should be reminded by mail, telephone, or other means of the need for vaccination.

Outpatient Facilities Providing Episodic or Acute Care

Beginning each September, acute health-care facilities (e.g., emergency departments and walk-in clinics) should offer vaccinations to persons for whom vaccination is recommended or provide written information regarding why, where, and how to obtain the vaccine. This written information should be available in languages appropriate for the populations served by the facility.

Nursing Homes and Other Residential Long-Term–Care Facilities

During October and November each year, vaccination should be routinely provided to all residents of chronic-care facilities with the concurrence of attending physicians. Consent for vaccination should be obtained from the resident or a family member at the time of admission to the facility or anytime afterwards. All residents should be vaccinated at one time, preceding the influenza season. Residents admitted through March after completion of the vaccination program at the facility should be vaccinated at the time of admission.

Acute-Care Hospitals

Persons of all ages (including children) with high-risk conditions and persons aged ≥50 years who are hospitalized at any time during September–March should be offered and strongly encouraged to receive influenza vaccine before they are discharged. In one study, 39%–46% of adult patients hospitalized during the winter with influenza-related diagnoses had been hospitalized during the preceding autumn (*240*). Thus, the hospital serves as a setting in which persons at increased risk for subsequent hospitalization can be identified and vaccinated. However, vaccination of persons at high risk during or after their hospitalizations is often not done. In a study of hospitalized Medicare patients, only 31.6% were vaccinated before admission, 1.9% during admission, and 10.6% after admission (*241*). Using standing orders in hospitals increases vaccination rates among hospitalized persons (*242*).

Visiting Nurses and Others Providing Home Care to Persons at High Risk

Beginning in September, nursing-care plans should identify patients for whom vaccination is recommended, and vac-

cine should be administered in the home, if necessary. Caregivers and other persons in the household (including children) should be referred for vaccination.

Other Facilities Providing Services to Persons Aged ≥50 Years

Beginning in October, such facilities as assisted living housing, retirement communities, and recreation centers should offer unvaccinated residents and attendees vaccination on-site before the influenza season. Staff education should emphasize the need for influenza vaccine.

Health-Care Workers

Beginning in October each year, health-care facilities should offer influenza vaccinations to all workers, including night and weekend staff. Particular emphasis should be placed on providing vaccinations to persons who care for members of groups at high risk. Efforts should be made to educate health-care workers regarding the benefits of vaccination and the potential health consequences of influenza illness for themselves, their family members, and their patients. All health-care workers should be provided convenient access to influenza vaccine at the work site, free of charge, as part of employee health programs (*127,137*).

Influenza Vaccine Supply

Influenza vaccine distribution delays or vaccine supply shortages have occurred in the United States vaccine in three of the last five influenza seasons. Influenza vaccine delivery delays or vaccine shortages remain possible in part because of the inherent critical time constraints in manufacturing the vaccine given the annual updating of the influenza vaccine strains. Steps being taken to accommodate possible future delays or vaccine shortages include identification and implementation of ways to expand the influenza vaccine supply and improvement of targeted delivery of vaccine to groups at high risk when delays or shortages are expected.

Influenza Vaccine Use During Shortages of Inactivated Vaccine

ACIP will publish additional guidance regarding the prioritized (tiered) use of inactivated influenza vaccine to be implemented only during periods when there is a shortage of influenza vaccine. Otherwise, when vaccine is in adequate supply, every effort should be made to promote and use influenza vaccine for all regularly targeted groups and for other persons who wish to reduce their risk for influenza illness. The prioritized (tiered) use of influenza vaccine during inactivated influenza vaccine shortages applies only to use of inactivated vaccine and not to LAIV. When feasible, during shortages of inactivated influenza vaccine, LAIV should be used preferentially for all healthy persons aged 5–49 years (including health-care workers) to increase the availability of inactivated vaccine for groups at high risk.

Future Directions for Influenza Vaccine Recommendations

ACIP plans to review new vaccination strategies for improving prevention and control of influenza, including the possibility of expanding recommendations for use of influenza vaccines. In addition, strategies for regularly monitoring vaccine effectiveness will be reviewed.

Recommendations for Using Antiviral Agents for Influenza

Antiviral drugs for influenza are an adjunct to influenza vaccine for controlling and preventing influenza. However, these agents are not a substitute for vaccination. Four licensed influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir.

Amantadine and rimantadine are chemically related antiviral drugs known as adamantanes with activity against influenza A viruses, but not influenza B viruses. Amantadine was approved in 1966 for chemoprophylaxis of influenza A (H2N2) infection and was later approved in 1976 for treatment and chemoprophylaxis of influenza type A virus infections among adults and children aged ≥1 year. Rimantadine was approved in 1993 for treatment and chemoprophylaxis of influenza A infection among adults and prophylaxis among children. Although rimantadine is approved only for chemoprophylaxis of influenza A infection among children, rimantadine treatment for influenza A among children can be beneficial (*243*).

Zanamivir and oseltamivir are chemically related antiviral drugs known as neuraminidase inhibitors that have activity against both influenza A and B viruses. Both zanamivir and oseltamivir were approved in 1999 for treating uncomplicated influenza infections. Zanamivir is approved for treating persons aged ≥7 years, and oseltamivir is approved for treatment of persons aged ≥1 year. In 2000, oseltamivir was approved for chemoprophylaxis of influenza among persons aged ≥13 years.

The four drugs differ in pharmacokinetics, side effects, routes of administration, approved age groups, dosages, and costs. An overview of the indications, use, administration, and known primary side effects of these medications is presented in the following sections. Information contained in this report might not represent FDA approval or approved labeling for the anti-

viral agents described. Package inserts should be consulted for additional information.

Role of Laboratory Diagnosis

Appropriate treatment of patients with respiratory illness depends on accurate and timely diagnosis. Early diagnosis of influenza can reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy. However, because certain bacterial infections can produce symptoms similar to influenza, bacterial infections should be considered and appropriately treated, if suspected. In addition, bacterial infections can occur as a complication of influenza.

Influenza surveillance information and diagnostic testing can aid clinical judgment and help guide treatment decisions. The accuracy of clinical diagnosis of influenza on the basis of symptoms alone is limited because symptoms from illness caused by other pathogens can overlap considerably with influenza (*30,34,35*). Influenza surveillance by state and local health departments and CDC can provide information regarding the presence of influenza viruses in the community. Surveillance can also identify the predominant circulating types, influenza A subtypes, and strains of influenza.

Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, polymerase chain reaction (PCR), and immunofluorescence assays (*25*). Sensitivity and specificity of any test for influenza might vary by the laboratory that performs the test, the type of test used, and the type of specimen tested. Among respiratory specimens for viral isolation or rapid detection, nasopharyngeal specimens are typically more effective than throat swab specimens (*244*). As with any diagnostic test, results should be evaluated in the context of other clinical and epidemiologic information available to health-care providers.

Commercial rapid diagnostic tests are available that can detect influenza viruses within 30 minutes (*25,245*). Some tests are approved for use in any outpatient setting, whereas others must be used in a moderately complex clinical laboratory. These rapid tests differ in the types of influenza viruses they can detect and whether they can distinguish between influenza types. Different tests can detect 1) only influenza A viruses; 2) both influenza A and B viruses, but not distinguish between the two types; or 3) both influenza A and B and distinguish between the two.

None of the tests provide any information about influenza A subtypes. The types of specimens acceptable for use (i.e., throat, nasopharyngeal, or nasal aspirates, swabs, or washes) also vary by test. The specificity and, in particular, the sensitivity of rapid tests are lower than for viral culture and vary by test (*246,247*). Because of the lower sensitivity of the rapid tests, physicians should consider confirming negative tests with viral culture or other means because of the possibility of false-negative rapid test results, especially during periods of peak community influenza activity. In contrast, false-positive rapid test results are less likely, but can occur during periods of low influenza activity. Therefore, when interpreting results of a rapid influenza test, physicians should consider the positive and negative predictive values of the test in the context of the level of influenza activity in their community. Package inserts and the laboratory performing the test should be consulted for more details regarding use of rapid diagnostic tests. Additional information concerning diagnostic testing is available at http://www.cdc.gov/flu/professionals/labdiagnosis.htm.

Despite the availability of rapid diagnostic tests, collecting clinical specimens for viral culture is critical, because only culture isolates can provide specific information regarding circulating strains and subtypes of influenza viruses. This information is needed to compare current circulating influenza strains with vaccine strains, to guide decisions regarding influenza treatment and chemoprophylaxis, and to formulate vaccine for the coming year. Virus isolates also are needed to monitor the emergence of antiviral resistance and the emergence of novel influenza A subtypes that might pose a pandemic threat.

Indications for Use

Treatment

When administered within 2 days of illness onset to otherwise healthy adults, amantadine and rimantadine can reduce the duration of uncomplicated influenza A illness, and zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day, compared with placebo (*75,248–265*). More clinical data are available concerning the efficacy of zanamivir and oseltamivir for treatment of influenza A infection than for treatment of influenza B infection (*253,266–281*). However, in vitro data and studies of treatment among mice and ferrets (*282–289*), in addition to clinical studies, have documented that zanamivir and oseltamivir have activity against influenza B viruses (*254,258–260,290,291*).

Data are limited regarding the effectiveness of the four antiviral agents in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases). Evidence for the effectiveness of these four antiviral drugs is principally based on studies of patients with uncomplicated influenza (*292*). Data are limited and inconclusive concerning the effectiveness of amantadine, rimantadine, zanamivir, and oseltamivir for treatment of influenza among persons at high risk for serious complications of influenza (*28,248,250,251,253,254,261,266–270*). One

study assessing oseltamivir treatment primarily among adults reported a reduction in complications, necessitating antibiotic therapy compared with placebo (*271*). Fewer studies of the efficacy of influenza antivirals have been conducted among pediatric populations (*248,251,257,258,267,272,273*). One study of oseltamivir treatment documented a decreased incidence of otitis media among children (*258*). Inadequate data exist regarding the safety and efficacy of any of the influenza antiviral drugs for use among children aged <1 year (*247*).

To reduce the emergence of antiviral drug-resistant viruses, amantadine or rimantadine therapy for persons with influenza A illness should be discontinued as soon as clinically warranted, typically after 3–5 days of treatment or within 24–48 hours after the disappearance of signs and symptoms. The recommended duration of treatment with either zanamivir or oseltamivir is 5 days.

Chemoprophylaxis

Chemoprophylactic drugs are not a substitute for vaccination, although they are critical adjuncts in preventing and controlling influenza. Both amantadine and rimantadine are indicated for chemoprophylaxis of influenza A infection, but not influenza B. Both drugs are approximately 60%–90% effective in preventing illness from influenza A infection (*75,248,267*). When used as prophylaxis, these antiviral agents can prevent illness while permitting subclinical infection and development of protective antibody against circulating influenza viruses. Therefore, certain persons who take these drugs will develop protective immune responses to circulating influenza viruses. Amantadine and rimantadine do not interfere with the antibody response to the vaccine (*248*). Both drugs have been studied extensively among nursing home populations as a component of influenza outbreak-control programs, which can limit the spread of influenza within chronic-care institutions (*248,266,274–276*).

Among the neuraminidase inhibitor antivirals zanamivir and oseltamivir, only oseltamivir has been approved for prophylaxis, but community studies of healthy adults indicate that both drugs are similarly effective in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%) (*253,277,293*). Both antiviral agents have also been reported to prevent influenza illness among persons administered chemoprophylaxis after a household member had influenza diagnosed (*278,290,293*). Experience with prophylactic use of these agents in institutional settings or among patients with chronic medical conditions is limited in comparison with the adamantanes (*260,269,270,279–281*). One 6-week study of oseltamivir prophylaxis among nursing home residents reported a 92% reduction in influenza illness (*260,294*). Use of zanamivir has not been reported to impair the immunologic response to influenza vaccine (*259,295*). Data are not available regarding the efficacy of any of the four antiviral agents in preventing influenza among severely immunocompromised persons.

When determining the timing and duration for administering influenza antiviral medications for prophylaxis, factors related to cost, compliance, and potential side effects should be considered. To be maximally effective as prophylaxis, the drug must be taken each day for the duration of influenza activity in the community. However, to be most cost-effective, one study of amantadine or rimantadine prophylaxis reported that the drugs should be taken only during the period of peak influenza activity in a community (*296*).

Persons at High Risk Who Are Vaccinated After Influenza Activity Has Begun. Persons at high risk for complications of influenza still can be vaccinated after an outbreak of influenza has begun in a community. However, development of antibodies in adults after vaccination takes approximately 2 weeks (*236,237*). When influenza vaccine is administered while influenza viruses are circulating, chemoprophylaxis should be considered for persons at high risk during the time from vaccination until immunity has developed. Children aged <9 years who receive influenza vaccine for the first time can require 6 weeks of prophylaxis (i.e., prophylaxis for 4 weeks after the first dose of vaccine and an additional 2 weeks of prophylaxis after the second dose).

Persons Who Provide Care to Those at High Risk. To reduce the spread of virus to persons at high risk during community or institutional outbreaks, chemoprophylaxis during peak influenza activity can be considered for unvaccinated persons who have frequent contact with persons at high risk. Persons with frequent contact include employees of hospitals, clinics, and chronic-care facilities, household members, visiting nurses, and volunteer workers. If an outbreak is caused by a variant strain of influenza that might not be controlled by the vaccine, chemoprophylaxis should be considered for all such persons, regardless of their vaccination status.

Persons Who Have Immune Deficiencies. Chemoprophylaxis can be considered for persons at high risk who are expected to have an inadequate antibody response to influenza vaccine. This category includes persons infected with HIV, chiefly those with advanced HIV disease. No published data are available concerning possible efficacy of chemoprophylaxis among persons with HIV infection or interactions with other drugs used to manage HIV infection. Such patients should be monitored closely if chemoprophylaxis is administered.

Other Persons. Chemoprophylaxis throughout the influenza season or during peak influenza activity might be appropriate for persons at high risk who should not be vaccinated.

Chemoprophylaxis can also be offered to persons who wish to avoid influenza illness. Health-care providers and patients should make this decision on an individual basis.

Control of Influenza Outbreaks in Institutions

Using antiviral drugs for treatment and prophylaxis of influenza is a key component of influenza outbreak control in institutions. In addition to antiviral medications, other outbreak-control measures include instituting droplet precautions and establishing cohorts of patients with confirmed or suspected influenza, re-offering influenza vaccinations to unvaccinated staff and patients, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients (*297–299*) (for additional information regarding outbreak control in specific settings, see Additional Information Regarding Influenza Infection Control Among Specific Populations).

The majority of published reports concerning use of antiviral agents to control influenza outbreaks in institutions are based on studies of influenza A outbreaks among nursing home populations where amantadine or rimantadine were used (*248,266,274–276,296*). Less information is available concerning use of neuraminidase inhibitors in influenza A or B institutional outbreaks (*269,270,281,294,300*). When confirmed or suspected outbreaks of influenza occur in institutions that house persons at high risk, chemoprophylaxis should be started as early as possible to reduce the spread of the virus. In these situations, having preapproved orders from physicians or plans to obtain orders for antiviral medications on short notice can substantially expedite administration of antiviral medications.

When outbreaks occur in institutions, chemoprophylaxis should be administered to all residents, regardless of whether they received influenza vaccinations during the previous fall, and should continue for a minimum of 2 weeks. If surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until approximately 1 week after the end of the outbreak. The dosage for each resident should be determined individually. Chemoprophylaxis also can be offered to unvaccinated staff who provide care to persons at high risk. Prophylaxis should be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influenza that is not well-matched by the vaccine.

In addition to nursing homes, chemoprophylaxis also can be considered for controlling influenza outbreaks in other closed or semiclosed settings (e.g., dormitories or other settings in which persons live in close proximity). For example, chemoprophylaxis with rimantadine has been used successfully to control an influenza A outbreak aboard a large cruise ship (*177*).

To limit the potential transmission of drug-resistant virus during outbreaks in institutions, whether in chronic or acute-care settings or other closed settings, measures should be taken to reduce contact as much as possible between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis (see Antiviral Drug-Resistant Strains of Influenza).

Dosage

Dosage recommendations vary by age group and medical conditions (Table 7).

Children

Amantadine. Use of amantadine among children aged <1 year has not been adequately evaluated. The FDA-approved dosage for children aged 1–9 years for treatment and prophylaxis is 4.4–8.8 mg/kg body weight/day, not to exceed 150 mg/day. Although further studies are needed to determine the optimal dosage for children aged 1–9 years, physicians should consider prescribing only 5 mg/kg body weight/day (not to exceed 150 mg/day) to reduce the risk for toxicity. The approved dosage for children aged ≥10 years is 200 mg/day (100 mg twice a day); however, for children weighing <40 kg, prescribing 5 mg/kg body weight/day, regardless of age, is advisable (*268*).

Rimantadine. Rimantadine is approved for prophylaxis among children aged ≥1 year and for treatment and prophylaxis among adults. Although rimantadine is approved only for prophylaxis of infection among children, certain specialists in the management of influenza consider it appropriate for treatment among children (*243*). Use of rimantadine among children aged <1 year has not been adequately evaluated. Rimantadine should be administered in 1 or 2 divided doses at a dosage of 5 mg/kg body weight/day, not to exceed 150 mg/day for children aged 1–9 years. The approved dosage for children aged ≥10 years is 200 mg/day (100 mg twice a day); however, for children weighing <40 kg, prescribing 5 mg/kg body weight/day, regardless of age, is recommended (*301*).

Zanamivir. Zanamivir is approved for treatment among children aged ≥7 years. The recommended dosage of zanamivir for treatment of influenza is two inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) (*259*).

Oseltamivir. Oseltamivir is approved for treatment among persons aged ≥1 year and for chemoprophylaxis among persons aged ≥13 years. Recommended treatment dosages for children vary by the weight of the child: the dosage recommendation for children who weigh ≤15 kg is 30 mg twice a day; for children weighing >15–23 kg, the dosage is 45 mg

TABLE 7. Recommended daily dosage of influenza antiviral medications for treatment and prophylaxis — United States

Antiviral agent	Age group (yrs) 1–6	7–9	10–12	13–64	≥65
Amantadine*					
Treatment, influenza A	5 mg/kg body weight/ day up to 150 mg in 2 divided doses†	5 mg/kg body weight/ day up to 150 mg in 2 divided doses†	100 mg twice daily§	100 mg twice daily§	≤100 mg/day
Prophylaxis, influenza A	5 mg/kg body weight/ day up to 150 mg in 2 divided doses†	5 mg/kg body weight/ day up to 150 mg in 2 divided doses†	100 mg twice daily§	100 mg twice daily§	≤100 mg/day
Rimantadine¶					
Treatment,** influenza A	NA††	NA	NA	100 mg twice daily§ §§	100 mg/day
Prophylaxis, influenza A	5 mg/kg body weight/ day up to 150 mg in 2 divided doses†	5 mg/kg body weight/ day up to 150 mg in 2 divided doses†	100 mg twice daily§	100 mg twice daily§	100 mg/day¶¶
Zanamivir* †††**					
Treatment, influenza A and B	NA	10 mg twice daily	10 mg twice daily	10 mg twice daily	10 mg twice daily
Oseltamivir					
Treatment,§§§ influenza A and B	Dose varies by child's weight¶¶¶	Dose varies by child's weight¶¶¶	Dose varies by child's weight¶¶¶	75 mg twice daily	75 mg twice daily
Prophylaxis, influenza A and B	NA	NA	NA	75 mg/day	75 mg/day

NOTE: Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel® — tablet and syrup); Geneva Pharms Tech (Amantadine HCL — capsule); USL Pharma (Amantadine HCL — capsule and tablet); and Alpharma, Carolina Medical, Copley Pharmaceutical, HiTech Pharma, Mikart, Morton Grove, and Pharmaceutical Associates (Amantadine HCL — syrup), and Sandoz. Rimantadine is manufactured by Forest Laboratories (Flumadine® — tablet and syrup); Corepharma, Impax Labs (Rimantadine HCL — tablet), and Amide Pharmaceuticals (Rimantadine HCL — tablet). Zanamivir is manufactured by GlaxoSmithKline (Relenza® — inhaled powder). Oseltamivir is manufactured by Roche Pharmaceuticals (Tamiflu® — tablet). This information is based on data published by the Food and Drug Administration (FDA), which is available at http://www.fda.gov.

* The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤50 mL/min/1.73m^2.

† 5 mg/kg body weight of amantadine or rimantadine syrup = 1 tsp/2.2 lbs.

§ Children aged ≥10 years who weigh <40 kg should be administered amantadine or rimantadine at a dosage of 5 mg/kg body weight/day.

¶ A reduction in dosage to 100 mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance ≤10 mL/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.

** Only approved by FDA for treatment among adults.

†† Not applicable.

§§ Rimantadine is approved by FDA for treatment among adults. However, certain specialists in the management of influenza consider rimantadine appropriate for treatment among children. Studies evaluating the efficacy of amantadine and rimantadine in children are limited, but they indicate that treatment with either drug diminishes the severity of influenza A infection when administered within 48 hours of illness onset (*243*).

¶¶ Older nursing-home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged ≥65 years, if they experience possible side effects when taking 200 mg/day.

*** Zanamivir administered through inhalation by using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device.

††† Zanamivir is not approved for prophylaxis.

§§§ A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance <30 mL/min.

¶¶¶ The dose recommendation for children who weigh ≤15 kg is 30 mg twice a day. For children who weigh >15–23 kg, the dose is 45 mg twice a day. For children who weigh >23–40 kg, the dose is 60 mg twice a day. And, for children who weigh >40 kg, the dose is 75 mg twice a day.

twice a day; for those weighing >23–40 kg, the dosage is 60 mg twice a day; and for children weighing >40 kg, the dosage is 75 mg twice a day. The treatment dosage for persons aged ≥13 years is 75 mg twice daily. For children aged ≥13 years, the recommended dose for prophylaxis is 75 mg once a day (*260*).

Persons Aged ≥65 Years

Amantadine. The daily dosage of amantadine for persons aged ≥65 years should not exceed 100 mg for prophylaxis or treatment, because renal function declines with increasing age. For certain older persons, the dose should be further reduced.

Rimantadine. Among older persons, the incidence and severity of central nervous system (CNS) side effects are substantially lower among those taking rimantadine at a dosage of 100 mg/day than among those taking amantadine at dosages adjusted for estimated renal clearance (*302*). However, chronically ill older persons have had a higher incidence of

CNS and gastrointestinal symptoms and serum concentrations 2–4 times higher than among healthy, younger persons when rimantadine has been administered at a dosage of 200 mg/day (*248*).

For prophylaxis among persons aged ≥65 years, the recommended dosage is 100 mg/day. For treatment of older persons in the community, a reduction in dosage to 100 mg/day should be considered if they experience side effects when taking a dosage of 200 mg/day. For treatment of older nursing home residents, the dosage of rimantadine should be reduced to 100 mg/day (*301*).

Zanamivir and Oseltamivir. No reduction in dosage is recommended on the basis of age alone.

Persons with Impaired Renal Function

Amantadine. A reduction in dosage is recommended for patients with creatinine clearance ≤50 mL/min. Guidelines for amantadine dosage on the basis of creatinine clearance are located in the package insert. Because recommended dosages on the basis of creatinine clearance might provide only an approximation of the optimal dose for a given patient, such persons should be observed carefully for adverse reactions. If necessary, further reduction in the dose or discontinuation of the drug might be indicated because of side effects. Hemodialysis contributes minimally to amantadine clearance (*303,304*).

Rimantadine. A reduction in dosage to 100 mg/day is recommended for persons with creatinine clearance <10 mL/min. Because of the potential for accumulation of rimantadine and its metabolites, patients with any degree of renal insufficiency, including older persons, should be monitored for adverse effects, and either the dosage should be reduced or the drug should be discontinued, if necessary. Hemodialysis contributes minimally to drug clearance (*305*).

Zanamivir. Limited data are available regarding the safety and efficacy of zanamivir for patients with impaired renal function. Among patients with renal failure who were administered a single intravenous dose of zanamivir, decreases in renal clearance, increases in half-life, and increased systemic exposure to zanamivir were observed (*259,306*). However, a limited number of healthy volunteers who were administered high doses of intravenous zanamivir tolerated systemic levels of zanamivir that were substantially higher than those resulting from administration of zanamivir by oral inhalation at the recommended dose (*307,308*). On the basis of these considerations, the manufacturer recommends no dose adjustment for inhaled zanamivir for a 5-day course of treatment for patients with either mild-to-moderate or severe impairment in renal function (*259*).

Oseltamivir. Serum concentrations of oseltamivir carboxylate (GS4071), the active metabolite of oseltamivir, increase with declining renal function (*260,309*). For patients with creatinine clearance of 10–30 mL/min (*260*), a reduction of the treatment dosage of oseltamivir to 75 mg once daily and in the prophylaxis dosage to 75 mg every other day is recommended. No treatment or prophylaxis dosing recommendations are available for patients undergoing routine renal dialysis treatment.

Persons with Liver Disease

Amantadine. No increase in adverse reactions to amantadine has been observed among persons with liver disease. Rare instances of reversible elevation of liver enzymes among patients receiving amantadine have been reported, although a specific relation between the drug and such changes has not been established (*310*).

Rimantadine. A reduction in dosage to 100 mg/day is recommended for persons with severe hepatic dysfunction.

Zanamivir and Oseltamivir. Neither of these medications has been studied among persons with hepatic dysfunction.

Persons with Seizure Disorders

Amantadine. An increased incidence of seizures has been reported among patients with a history of seizure disorders who have received amantadine (*311*). Patients with seizure disorders should be observed closely for possible increased seizure activity when taking amantadine.

Rimantadine. Seizures (or seizure-like activity) have been reported among persons with a history of seizures who were not receiving anticonvulsant medication while taking rimantadine (*312*). The extent to which rimantadine might increase the incidence of seizures among persons with seizure disorders has not been adequately evaluated.

Zanamivir and Oseltamivir. Seizure events have been reported during postmarketing use of zanamivir and oseltamivir, although no epidemiologic studies have reported any increased risk for seizures with either zanamivir or oseltamivir use.

Route

Amantadine, rimantadine, and oseltamivir are administered orally. Amantadine and rimantadine are available in tablet or syrup form, and oseltamivir is available in capsule or oral suspension form. Zanamivir is available as a dry powder that is self-administered via oral inhalation by using a plastic device included in the package with the medication. Patients will benefit from instruction and demonstration of correct use of this device.

Pharmacokinetics

Amantadine

Approximately 90% of amantadine is excreted unchanged in the urine by glomerular filtration and tubular secretion (*274,313–316*). Thus, renal clearance of amantadine is reduced substantially among persons with renal insufficiency, and dosages might need to be decreased (see Dosage) (Table 7).

Rimantadine

Approximately 75% of rimantadine is metabolized by the liver (*267*). The safety and pharmacokinetics of rimantadine among persons with liver disease have been evaluated only after single-dose administration (*267,317*). In a study of persons with chronic liver disease (the majority with stabilized cirrhosis), no alterations in liver function were observed after a single dose. However, for persons with severe liver dysfunction, the apparent clearance of rimantadine was 50% lower than that reported for persons without liver disease (*302*).

Rimantadine and its metabolites are excreted by the kidneys. The safety and pharmacokinetics of rimantadine among patients with renal insufficiency have been evaluated only after single-dose administration (*267,305*). Further studies are needed to determine multiple-dose pharmacokinetics and the most appropriate dosages for patients with renal insufficiency. In a single-dose study of patients with anuric renal failure, the apparent clearance of rimantadine was approximately 40% lower, and the elimination half-life was approximately 1.6-fold greater than that among healthy persons of the same age (*305*). Hemodialysis did not contribute to drug clearance. In studies of persons with less severe renal disease, drug clearance was also reduced, and plasma concentrations were higher than those among control patients without renal disease who were the same weight, age, and sex (*301,317*).

Zanamivir

In studies of healthy volunteers, approximately 7%–21% of the orally inhaled zanamivir dose reached the lungs, and 70%–87% was deposited in the oropharynx (*259,318*). Approximately 4%–17% of the total amount of orally inhaled zanamivir is systemically absorbed. Systemically absorbed zanamivir has a half-life of 2.5–5.1 hours and is excreted unchanged in the urine. Unabsorbed drug is excreted in the feces (*259,308*).

Oseltamivir

Approximately 80% of orally administered oseltamivir is absorbed systemically (*309*). Absorbed oseltamivir is metabolized to oseltamivir carboxylate, the active neuraminidase inhibitor, primarily by hepatic esterases. Oseltamivir carboxylate has a half-life of 6–10 hours and is excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway (*260,319*). Unmetabolized oseltamivir also is excreted in the urine by glomerular filtration and tubular secretion (*320*).

Side Effects and Adverse Reactions

When considering use of influenza antiviral medications (i.e., choice of antiviral drug, dosage, and duration of therapy), clinicians must consider the patient's age, weight, and renal function (Table 7); presence of other medical conditions; indications for use (i.e., prophylaxis or therapy); and the potential for interaction with other medications.

Amantadine and Rimantadine

Both amantadine and rimantadine can cause CNS and gastrointestinal side effects when administered to young, healthy adults at equivalent dosages of 200 mg/day. However, incidence of CNS side effects (e.g., nervousness, anxiety, insomnia, difficulty concentrating, and lightheadedness) is higher among persons taking amantadine than among those taking rimantadine (*320*). In a 6-week study of prophylaxis among healthy adults, approximately 6% of participants taking rimantadine at a dosage of 200 mg/day experienced one or more CNS symptoms, compared with approximately 13% of those taking the same dosage of amantadine and 4% of those taking placebo (*320*). A study of older persons also demonstrated fewer CNS side effects associated with rimantadine compared with amantadine (*302*). Gastrointestinal side effects (e.g., nausea and anorexia) occur among approximately 1%–3% of persons taking either drug, compared with 1% of persons receiving the placebo (*320*).

Side effects associated with amantadine and rimantadine are usually mild and cease soon after discontinuing the drug. Side effects can diminish or disappear after the first week, despite continued drug ingestion. However, serious side effects have been observed (e.g., marked behavioral changes, delirium, hallucinations, agitation, and seizures) (*303,311*). These more severe side effects have been associated with high plasma drug concentrations and have been observed most often among persons who have renal insufficiency, seizure disorders, or certain psychiatric disorders and among older persons who have been taking amantadine as prophylaxis at a dosage of 200 mg/day (*274*). Clinical observations and studies have indicated that lowering the dosage of amantadine among these persons reduces the incidence and severity of such side effects (Table 7). In acute overdosage of amantadine, CNS, renal, respiratory, and cardiac toxicity, including arrhythmias, have been reported (*303*). Because rimantadine has been marketed for a shorter period than amantadine, its

safety among certain patient populations (e.g., chronically ill and older persons) has been evaluated less frequently. Because amantadine has anticholinergic effects and might cause mydriasis, it should not be used among patients with untreated angle closure glaucoma (*303*).

Zanamivir

In a study of zanamivir treatment of ILI among persons with asthma or chronic obstructive pulmonary disease where study medication was administered after use of a B2-agonist, 13% of patients receiving zanamivir and 14% of patients who received placebo (inhaled powdered lactose vehicle) experienced a >20% decline in forced expiratory volume in 1 second (FEV1) after treatment (*259,261*). However, in a phase-I study of persons with mild or moderate asthma who did not have ILI, one of 13 patients experienced bronchospasm after administration of zanamivir (*259*). In addition, during postmarketing surveillance, cases of respiratory function deterioration after inhalation of zanamivir have been reported. Certain patients had underlying airway disease (e.g., asthma or chronic obstructive pulmonary disease). Because of the risk for serious adverse events and because the efficacy has not been demonstrated among this population, zanamivir is not recommended for treatment for patients with underlying airway disease (*259*). If physicians decide to prescribe zanamivir to patients with underlying chronic respiratory disease after carefully considering potential risks and benefits, the drug should be used with caution under conditions of appropriate monitoring and supportive care, including the availability of short-acting bronchodilators (*292*). Patients with asthma or chronic obstructive pulmonary disease who use zanamivir are advised to 1) have a fast-acting inhaled bronchodilator available when inhaling zanamivir and 2) stop using zanamivir and contact their physician if they experience difficulty breathing (*259*). No definitive evidence is available regarding the safety or efficacy of zanamivir for persons with underlying respiratory or cardiac disease or for persons with complications of acute influenza (*292*). Allergic reactions, including oropharyngeal or facial edema, have also been reported during postmarketing surveillance (*259,269*).

In clinical treatment studies of persons with uncomplicated influenza, the frequencies of adverse events were similar for persons receiving inhaled zanamivir and for those receiving placebo (i.e., inhaled lactose vehicle alone) (*249–254,269*). The most common adverse events reported by both groups were diarrhea; nausea; sinusitis; nasal signs and symptoms; bronchitis; cough; headache; dizziness; and ear, nose, and throat infections. Each of these symptoms was reported by <5% of persons in the clinical treatment studies combined (*259*).

Oseltamivir

Nausea and vomiting were reported more frequently among adults receiving oseltamivir for treatment (nausea without vomiting, approximately 10%; vomiting, approximately 9%) than among persons receiving placebo (nausea without vomiting, approximately 6%; vomiting, approximately 3%) (*255,256,260,321*). Among children treated with oseltamivir, 14.3% had vomiting, compared with 8.5% of placebo recipients. Overall, 1% discontinued the drug secondary to this side effect (*258*), whereas a limited number of adults who were enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms (*260*). Similar types and rates of adverse events were reported in studies of oseltamivir prophylaxis (*260*). Nausea and vomiting might be less severe if oseltamivir is taken with food (*260,321*).

Use During Pregnancy

No clinical studies have been conducted regarding the safety or efficacy of amantadine, rimantadine, zanamivir, or oseltamivir for pregnant women; only two cases of amantadine use for severe influenza illness during the third trimester have been reported (*144,145*). However, both amantadine and rimantadine have been demonstrated in animal studies to be teratogenic and embryotoxic when administered at substantially high doses (*301,303*). Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these four drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus (see manufacturers' package inserts) (*259,260,301,303*).

Drug Interactions

Careful observation is advised when amantadine is administered concurrently with drugs that affect CNS, including CNS stimulants. Concomitant administration of antihistamines or anticholinergic drugs can increase the incidence of adverse CNS reactions (*248*). No clinically substantial interactions between rimantadine and other drugs have been identified.

Clinical data are limited regarding drug interactions with zanamivir. However, no known drug interactions have been reported, and no clinically critical drug interactions have been predicted on the basis of in vitro data and data from studies using rats (*259,322*).

Limited clinical data are available regarding drug interactions with oseltamivir. Because oseltamivir and oseltamivir carboxylate are excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway, a potential exists for interaction with other agents excreted by this pathway.

For example, coadministration of oseltamivir and probenecid resulted in reduced clearance of oseltamivir carboxylate by approximately 50% and a corresponding approximate two-fold increase in the plasma levels of oseltamivir carboxylate (*260,319*).

No published data are available concerning the safety or efficacy of using combinations of any of these four influenza antiviral drugs. For more detailed information concerning potential drug interactions for any of these influenza antiviral drugs, package inserts should be consulted.

Antiviral Drug-Resistant Strains of Influenza

Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa (*323*). Drug-resistant viruses can appear in approximately one third of patients when either amantadine or rimantadine is used for therapy (*273,323,324*). During the course of amantadine or rimantadine therapy, resistant influenza strains can replace susceptible strains within 2–3 days of starting therapy (*325,326*). Resistant viruses have been isolated from persons who live at home or in an institution where other residents are taking or have recently taken amantadine or rimantadine as therapy (*327,328*); however, the frequency with which resistant viruses are transmitted and their effect on efforts to control influenza are unknown. Amantadine- and rimantadine-resistant viruses are not more virulent or transmissible than susceptible viruses (*329*). The screening of epidemic strains of influenza A has rarely detected amantadine- and rimantadine-resistant viruses (*325,330,331*).

Persons who have influenza A infection and who are treated with either amantadine or rimantadine can shed susceptible viruses early in the course of treatment and later shed drug-resistant viruses, including after 5–7 days of therapy (*273*). Such persons can benefit from therapy even when resistant viruses emerge.

Resistance to zanamivir and oseltamivir can be induced in influenza A and B viruses in vitro (*332–339*), but induction of resistance usually requires multiple passages in cell culture. By contrast, resistance to amantadine and rimantadine in vitro can be induced with fewer passages in cell culture (*340,341*). Development of viral resistance to zanamivir and oseltamivir during treatment has been identified but does not appear to be frequent (*260,342–345*). In one pediatric study, 5.5% of patients treated with oseltamivir had posttreatment isolates that were resistant to neuraminidase inhibitors. One limited study of Japanese children treated with oseltamivir reported a high frequency of resistant viruses (*346*). However, no transmission of neuraminidase inhibitor resistant viruses in humans has been documented to date. No isolates with reduced susceptibility to zanamivir have been reported from clinical trials, although the number of posttreatment isolates tested is limited (*347*), and the risk for emergence of zanamivir-resistant isolates cannot be quantified (*259*). Only one clinical isolate with reduced susceptibility to zanamivir, obtained from an immunocompromised child on prolonged therapy, has been reported (*343*). Available diagnostic tests are not optimal for detecting clinical resistance to the neuraminidase inhibitor antiviral drugs, and additional tests are being developed (*347,348*). Postmarketing surveillance for neuraminidase inhibitor-resistant influenza viruses is being conducted (*349*).

Sources of Information Regarding Influenza and Its Surveillance

Information regarding influenza surveillance, prevention, detection, and control is available at http://www.cdc.gov/flu/weekly/fluactivity.htm. Surveillance information is available through the CDC Voice Information System (influenza update) at 888-232-3228 or CDC Fax Information Service at 888-232-3299. During October–May, surveillance information is updated at least every other week. In addition, periodic updates regarding influenza are published in the *MMWR Weekly Report* (http://www.cdc.gov/mmwr). Additional information regarding influenza vaccine can be obtained by calling 800-CDC-INFO (800-232-4636). State and local health departments should be consulted concerning availability of influenza vaccine, access to vaccination programs, information related to state or local influenza activity, and for reporting influenza outbreaks and receiving advice concerning outbreak control.

Additional Information Regarding Influenza Infection Control Among Specific Populations

Each year, ACIP provides general, annually updated information regarding control and prevention of influenza. Other reports related to controlling and preventing influenza among specific populations (e.g., immunocompromised persons, health-care workers, hospitals, and travelers) are also available in the following publications:

- CDC. Recommended adult immunization schedule—United States, 2004–05. MMWR 2004;53:Q1–4.
- Garner JS, Hospital Infection Control Practices Advisory Committee. Guideline for isolation precautions in hospitals. Infect Control Hosp Epidemiol 1996;17:53–80.

- CDC. Guidelines for preventing health-care–associated pneumonia, 2003: recommendations of CDC and the Health-care Infection Control Practices Advisory Committee. MMWR 2003;53(No. RR-3):1–36.
- Bolyard EA, Tablan OC, Williams WW, et al., Hospital Infection Control Practices Advisory Committee. Guideline for infection control in health-care personnel. Am J Infect Control 1998;26:289–354.
- CDC. Respiratory hygiene/cough etiquette in health-care settings. Atlanta, GA: US Department of Health and Human Services, CDC, 2003. Available at http://www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm.
- Bradley SF. The Long-Term–Care Committee of the Society for Health-care Epidemiology of America. Prevention of influenza in long-term care facilities. Infect Control Hosp Epidemiol 1999;20:629–37.
- Sneller V-P, Izurieta H, Bridges C, et al. Prevention and control of vaccine-preventable diseases in long-term care facilities. Journal of the American Medical Directors Association 2000;1(Suppl):S2–37.
- American Academy of Pediatrics. 2003 red book: report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003.
- CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Practitioners (AAFP). MMWR 2002;51(No. RR-2):1–35.
- Bodnar UR, Maloney SA, Fielding KL, et al. Preliminary guidelines for the prevention and control of influenza-like illness among passengers and crew members on cruise ships. Atlanta, GA: US Department of Health and Human Services, CDC, National Center for Infectious Diseases; 1999.
- CDC. General recommendations for preventing influenza A infection among travelers. Atlanta, GA: US Department of Health and Human Services, CDC; 2003. Available at http://www2.ncid.cdc.gov/travel/yb/utils/ybGet.asp?section=dis&obj=influenza.htm.
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